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The Royal College of Physicians and Surgeons of Glasgow
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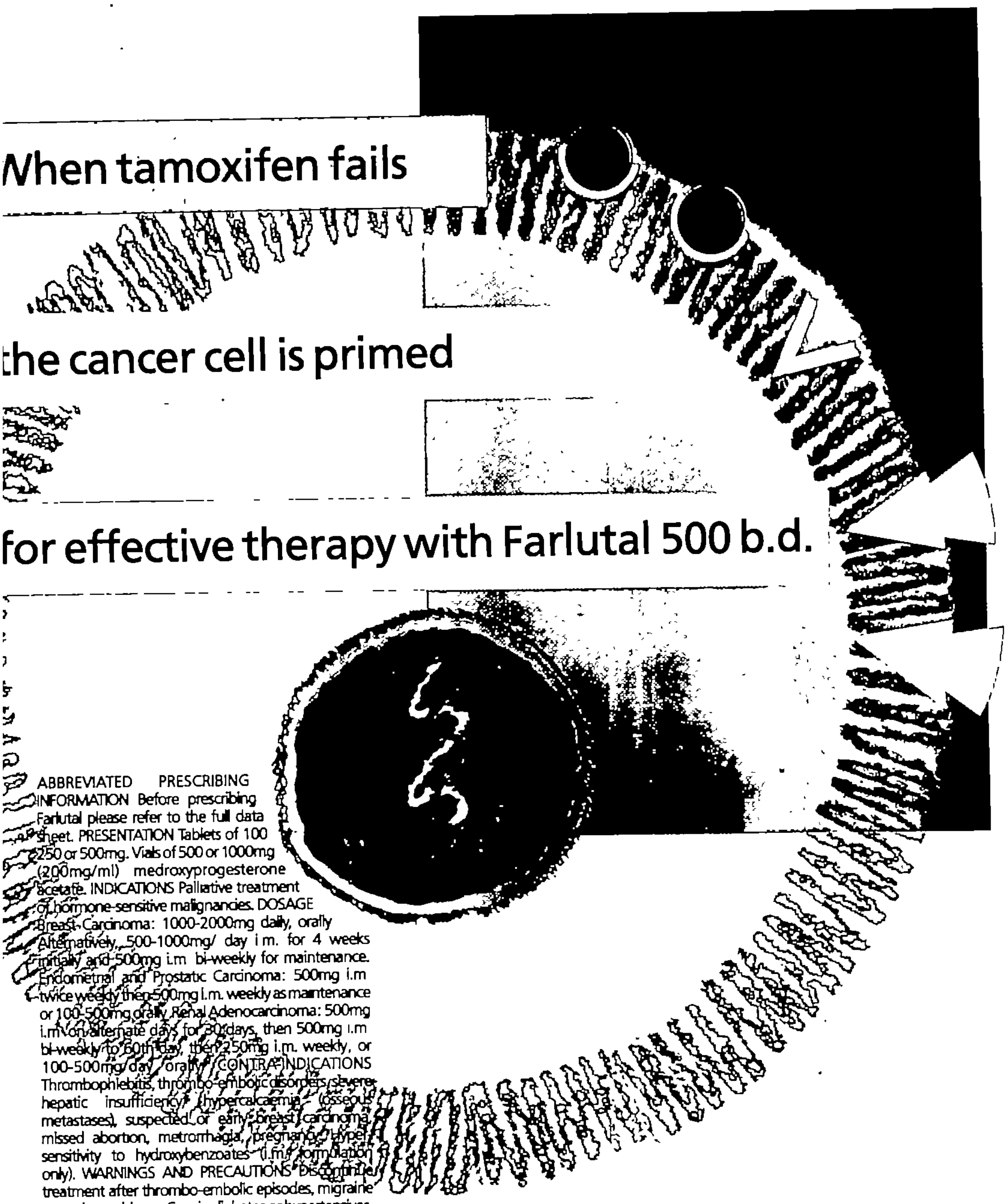

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Leading article

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Venous anatomy of the lower oesophagus: a new perspective on varices

The first reported case of ruptured oesophageal varices is generally accredited to Fauvel[1] who reported a 39-year-old alcoholic man who had died in April 1831 with profuse haematemesis. He stated that the mucous membrane of the lower two-thirds of the oesophagus was elevated by varices which in some places were as large as a goose quill. Despite considerable research during the past 100 years an enigma remains. Why does variceal rupture nearly always occur in the distal oesophagus? Autopsy[2], endoscopy[3,4] and surgical studies[5] indicate that the bleeding source is usually in the distal 5 cm of the oesophagus[6]. Both the Belfast[7] and Cape Town[8] groups have noted the efficacy of injection sclerotherapy confined to the distal oesophagus in the control of variceal haemorrhage. There is no evidence that oesophagitis is the precipitating cause of bleeding[9] and the venous anatomy of the lower oesophagus has been re-examined recently. An important early study of the venous anatomy of the lower oesophagus was conducted by Butler[10] using injection techniques. He studied mainly fetuses and described: an intrinsic plexus subdivided into a subepithelial plexus in the lamina propria; a submucous plexus outside the muscularis mucosa and perforating veins which pierced the muscular wall of the oesophagus; venae comitantes of the vagi running in the adventitial layer of the oesophagus and extrinsic veins formed by perforating veins. In a later study he noted that oesophageal varices were most prominent subepithelially in the juxtacardiac region[11] and these findings were later confirmed in an autopsy study by Macbeth[12]. De Carvalho[13] showed that the veins of the distal oesophagus are situated mainly in the mucosa and run in longitudinal palisades extending 1·5–3·5 cm from the epithelial line. Above and below this region the veins seemed to be chiefly in the submucosa and De Carvalho suggested that this arrangement of veins at the oesophagogastric junction may help to prevent reflux.

More recently, using a Doppler ultrasound probe passed through an endoscope McCormack *et al.*[14] have demonstrated that there is a fairly constant perforating vein which runs from the perioesophageal plexus to the subepithelial and submucosal layers at 36 cm. Image analysis systems have shown that in the distal 5 cm of the oesophagus a significantly greater proportion of the lamina propria is occupied by veins when this area is compared with the more proximal oesophagus or stomach[15]. In a reciprocal fashion, the submucosa of the stomach and proximal oesophagus contains a relatively greater proportion of veins when compared with the distal oesophagus. Further analysis has revealed that the differences in the area occupied by veins in the distal oesophagus is due to an increase in both the number and size of veins in the lamina propria. A Japanese study using similar techniques has confirmed this arrangement of veins in the distal oesophagus, and the distal 4 cm of the oesophagus has been termed the 'critical area'[16]. This area corresponds to the high pressure zone which has recently been shown to contain an area of thickened muscle[17]. Teleologically it may be that local increase in muscle and pressure 'force' the veins to become more superficial and explain the propensity for varices to bleed from this area.

Recently, the Cape Town Group have studied the lower oesophageal venous anatomy using a refined resin-casting technique[18]. Four layers of veins are described: intra-epithelial channels, a superficial venous plexus, deep intrinsic veins and adventitial veins. The intra-epithelial channels probably correspond to the vascular epithelial channels seen in oesophageal transection rings[19] and may correspond to the cherry-red spots of the Japanese literature[20]. The Cape Town study[18] also confirms the presence of perforating veins in the distal oesophagus. The superficial venous plexus communicates with the gastric venous plexus and the deep intrinsic veins form the varices in portal hypertension. These varices appear to lie in three to five main trunks which have multiple communications with the superficial venous plexus.

In the light of these anatomical studies, we suggest that minor variceal bleeds may be due to rupture of an intra-epithelial channel (perhaps provoked by a sudden rise in pressure) or to bleeding from the superficial venous plexus. Major bleeds are probably due to disruption of one of the larger deep venous trunks. Intravariceal sclerotherapy

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probably acts by thrombosing the main venous trunks with their connection to the superficial venous plexus and hence to intra-epithelial channels. The constant perforating veins of the distal oesophagus and interconnections between layers of veins explain the re-appearance of varices after eradication[21]. Paravariceal sclerotherapy may act by thrombosing the smaller superficial venous plexus or by thickening the mucosa due to fibrosis. Recent studies of the lower oesophagus have clarified the detailed anatomy of the critical zone of bleeding, and provide a clue to the pathogenesis of variceal rupture. They also provide an explanation for the early success of injection and for the frequent recurrence of varices after their eradication by sclerotherapy.

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Surgical treatment of chronic pancreatitis: an overview

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The correct management of chronic pancreatitis remains undecided. The aims of surgical treatment are to relieve pain, treat complications and preserve pancreatic function. The appropriate surgical procedure to achieve these ends must be carefully chosen.

> 'The feasibility of an operation is
> not an indication for its performance.'
> Lord Cohen of Birkenhead

Surgical treatment of chronic pancreatitis remains a major challenge. Nothing is more distressing for the patient and relatives than to find that, following the trauma of a major operation, the symptoms have not been relieved. It is also rather disturbing to a surgeon's ego when he realizes that his technically perfect and time-consuming operation has not benefited the patient's symptoms or duration of survival. Thus, the four major issues are selection of the patient for operation, selection of the surgeon, the timing of operation, and the choice of operative procedure.

The aetiology of chronic pancreatitis is alcoholism in the vast majority of instances. However, it is essential to identify the occasional patient with an unusual cause. The need to recognize that an underlying pancreatic or periampullary cancer may give rise to chronic pancreatitis should be emphasized, especially in middle-aged women who deny a history of alcoholism. Congenital anomalies of the duodenum, bile duct and pancreatic duct, may result in chronic pancreatitis which is largely focal and confined to the head and uncinate process of the gland and is thus potentially curable by a timely resection of the Whipple type. Blunt abdominal trauma may lead to significant ductal injury and cicatrization in the body of the pancreas leading to chronic pancreatitis which is confined to the body and tail of the gland. Distal pancreatectomy with splenectomy is curative. The very rare entity of hereditary pancreatitis is mentioned only to reiterate the need for careful follow-up because of the high incidence of subsequent pancreatic cancer in these individuals. This author has never seen a documented case of chronic pancreatitis due to hyperparathyroidism, although this association is mentioned in nearly every textbook. Gallstones are never a cause of chronic pancreatitis. The incidence of gallstones in patients with chronic pancreatitis is exactly the same as in the general population. Cholecystectomy will not influence the course of the disease and should be advocated on its own clinical merits, namely, to avoid diagnostic confusion and to prevent biliary complications. Pancreas divisum is an anatomical variant which may or may not cause recurrent acute pancreatitis which may or may not evolve into focal pancreatitis in the head of the gland. The incidence of pancreas divisum in patients with chronic pancreatitis is the same as in the general population; hence, there are no data to incriminate pancreas divisum as a cause of chronic pancreatitis. Patients with hyperlipidaemia often develop mild, self-limiting recurrent attacks of acute pancreatitis. This can be adequately controlled by appropriate medical management of the underlying metabolic disorder and rarely, if ever, progresses to chronic pancreatitis.

Life expectancy of patients with chronic pancreatitis

Once a patient has established chronic pancreatitis his/her life expectancy must be taken into consideration in the planning of a treatment strategy. In this author's opinion, treatment must be considered more as palliation than as cure in the vast majority of instances. Although chronic pancreatitis is a benign disease, the duration of survival of afflicted individuals does not follow a benign pattern. Many reports acknowledge a high incidence of 'late deaths' which increases with time[1]. Although most authors refrain from classifying death as a 'poor result', the common practice of calculating survival by excluding all deaths from the denominator at every point in time should be strongly discouraged since it often gives a false impression that the early and late results are similar when they definitely are not.

Continuing alcoholism and metabolic complications contribute largely to the patients' demise. About 25–35 per cent of patients operated upon for chronic pancreatitis are dead at 4–6 years. This incidence of late deaths increases to 38 per cent after 10 years and to 42 per cent at 12 years[2–6]. Prinz and Greenlee reported that 53 per cent of their patients died at 1–20 years (mean 6 years) following operation; 63 per cent of the patients who continued drinking alcohol died compared with 25 per cent in the reformed group[4]. Leger *et al.* found that 80 per cent of the 'late death' patients had continued to drink alcohol[3]. They also reported that patients with poor early results died before the others, but this correlation between poor early results and late deaths has not been substantiated by other authorities.

It must be emphasized that these dismal data are based largely or exclusively on patients with alcoholic chronic pancreatitis and cannot be extrapolated to predict the results of operation on patients with non-alcoholic pancreatitis.

Is surgical treatment of chronic pancreatitis for pain relief warranted?

Ammann and his colleagues have proposed the thesis that there is no place for surgical treatment of chronic pancreatitis for pain relief[7,8]. They believed that spontaneous pain relief occurs with time as the pancreatitis 'burns out'. They followed a group of 163 patients with chronic pancreatitis, 87 of whom underwent medical treatment and 76 surgical therapy of all types. They reported that pain relief occurred at a similar rate for both the operated and the unoperated groups. They observed that pain relief was unrelated to therapy but was related to a significant increase in pancreatic dysfunction or calcification, with maximal relief occurring at a median of 4·3 years from the onset of the disease. In reply, Bradley has quite rightly pointed out the two main problems with this study, namely adverse patient selection for operation and employment of ineffective surgical

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procedures[9]. Patients in the surgical group underwent a variety of procedures including pancreaticojejunostomy, partial pancreatic resection, papillotomy and drainage of pseudocysts; several of these surgical procedures have been abandoned by most surgeons as ineffective for pain relief.

Scuro *et al.* compared 93 patients with chronic pancreatitis who underwent lateral pancreaticojejunostomy to 98 patients selected for medical management[10]. At 10 years, pain relief was obtained in 62·2 per cent of the surgical patients and 42·8 per cent of the medical patients. Strict comparison between the two groups, however, could not be justified since the surgical patients had apparently experienced more pain before operation and were all demonstrated to have marked dilatation of the main pancreatic duct. Jordan *et al.* observed that only 6 per cent of 74 alcoholic patients managed non-surgically developed any spontaneous pain relief with time[2]. It is indeed difficult to espouse the theory of 'burned out' pancreatitis as a basis for pain relief since, if this were true, the results of drainage procedures on the pancreatic duct would improve with time. The universal surgical experience is just the opposite, namely that pain relief obtained after drainage procedures is not maintained with time. Clearly, properly stratified prospective randomized studies comparing medical and surgical therapy are required to resolve this debate. In the meantime, surgical therapy cannot ethically be withheld from an individual patient with intractable pain who can be potentially rehabilitated.

A surgical philosophy

The aims of surgical treatment remain threefold:

1. To relieve intractable pain.
2. To treat complications, especially if they are potentially life-threatening.
3. To preserve functioning pancreatic tissue.

These goals must be achieved at the lowest operative risk. Before embarking on any surgical procedure for chronic pancreatitis, both the surgeon and the patient must face some hard realities. These can be summarized as follows:

1. By definition, chronic pancreatitis implies a *progressive irreversible* loss of glandular (exocrine and endocrine) function and this relentless deterioration is *unaffected* by any surgical procedure.
2. There is no one perfect operation that is applicable to all patients suffering from chronic pancreatitis.
3. None of the various operations recommended have consistently achieved the desired result.
4. The unreformed alcoholic or drug addict has a very limited life expectancy. He is a poor candidate from the point of view of mortality and morbidity for any major operation and also experiences the worst overall results[11].
5. Any operation recommended for pain has to be distinguished from that performed for a complication of the disease.
6. The complete lack of uniformity in the selection of patients or operative procedures, in the evaluation of results, and in follow-up, makes it near impossible to compare various approaches to the disease[12]. Most importantly, chronic pancreatitis afflicts a heterogenous population the world over. Social and cultural factors are important and do affect surgical results. Even in the same country the individual surgeon is a 'victim' of his own referral practice, the type of institution where he practises, and the general population in the catchment area of his hospital. Thus, the results obtained from a Veterans Administration Medical Center, a county hospital, a university hospital, and a private clinic, are not comparable and cannot be expected to be similar.
7. Re-operations on the pancreas are always hazardous, even for the most skilful surgeon, and the degree of technical difficulty increases with the number of preceding operations on the gland[13].

Selection of patients

Any patient selected to have an operation for chronic pancreatitis must have a planned rehabilitation starting well in advance of the surgical procedure. This should involve appropriately interested social workers, psychiatrists, selected family members, and various associations such as Alcoholics Anonymous. Any nutritional and metabolic disturbance must be corrected before the operation. Postoperative complications including delirium tremens, withdrawal symptoms, and various types of psychoses must be anticipated and dealt with.

Choice of operative procedures

Indirect operations on the biliary tract, such as gastrointestinal diversion or exclusion, nerve interruptions and parathyroid removal are mentioned only to be condemned[6,14–17]. These are, at best, only of historic interest. Direct operation on the pancreas is the best we have to offer and generally includes drainage procedures (of cysts or of a dilated main pancreatic duct), pancreatic resections of various magnitudes, and combinations of resection and drainage. The general guideline is that the surgeon should be conservative whenever there is residual endocrine and exocrine function and whenever there is a dilated duct of Wirsung (greater than 8 mm diameter). The surgeon can justify being radical if there is a suspicion of cancer (usually exhibited by localized mass or compression of adjacent organs), if there is exocrine and endocrine insufficiency, and if there is extensive glandular destruction by sclerosis, calcifications, or multiple cysts. It is always a tragedy if a non-reformed alcoholic drug addict is converted into an insulin-requiring diabetic by a major pancreatic resection since the patient's already limited life expectancy is bound to be shortened further. As a general rule, avoidance of alcohol and rehabilitation of the patient are more important determinants of outcome after operation than the type of operation itself[18].

What are the realities? The surgeon must never operate out of desperation or frustration. He must always understand his limitations. It is worth reiterating that both drainage procedures and partial extirpation of the gland are irrational procedures.

Operations for pain

Duct drainage procedures

The rationale for duct drainage procedures is that pain is a consequence of outflow resistance to pancreatic secretion. This thesis is probably untrue and has certainly never been proven. Ductal dilatation in chronic pancreatitis is rarely due to a mechanical obstruction. Ductal pressures have seldom been measured and the reported results have not been uniformly concordant. Retrograde pancreatography usually shows free unobstructed flow from the large ducts. Thus, it is safe to say that duct 'drainage' is not synonymous with duct 'decompression'. Hence, the benefits of duct drainage procedures are difficult to explain.

Attacks on the sphincters of Oddi and Wirsung. At best, only 60 per cent of patients with chronic pancreatitis have a dilated pancreatic ductal system. If the dilatation is uniform with a localized ampullary obstruction, which is a rarity in this author's experience, such local ampullary obstruction can be dealt with in the first instance by a sphincteroplasty. Even when the operation is used selectively, the long-term results are dubious. Fifty per cent of patients are said to have pain relief at 5 years but this author is sceptical about such claims[19–23].

Probably the best critical analysis of double sphincteroplasty (section of the sphincters of Oddi and Wirsung) was reported by Bagley *et al.*[19]. They studied 67 patients with laboratory evidence of pancreatitis who had disabling pain but had only *minimal* ductal changes on pancreatography and *minimal* parenchymal evidence of disease at operation. The operative mortality was 3 per cent and pain relief was obtained in 66 per cent of patients at 6 months, 48 per cent at 2 years and

43 per cent at 5 years respectively. The most telling part of this report is that 11 (90 per cent) of 12 patients who gave up alcohol remained free of pain compared with only 2 (13 per cent) of 16 patients who continued to consume alcohol.

Attack on the main pancreatic duct. Retrograde (distal) duct drainage into a Roux-en-Y loop of jejunum following distal transection of the gland and splenectomy is usually associated with prominent names in American surgery, namely DuVal, Longmire and Zollinger[24,25]. However, the operation has been abandoned because it does not provide long-term pain relief. Stenosis of the anastomosis is common and it is now fashionable to worry about post-splenectomy sepsis. Puestow and Gillesby attributed failures of this operation to the presence of multiple proximal strictures and extended the operation by unroofing the main duct along its length before its insertion into the Roux-en-Y loop of jejunum[26].

Partington and Rochelle[27] and Thal[28] further modified Puestow's approach and developed an anterior sutured anastomosis between the Roux-en-Y loop of jejunum and the unroofed duct of Wirsung in side-to-side fashion. This clearly provided better drainage of the pancreatic duct, especially when the pancreatic incision is carried into the head to ensure drainage of the head and uncinate process. It also avoids extensive pancreatic and peripancreatic dissection and obviates the need for a splenectomy.

This lateral pancreaticojejunostomy (Puestow/Partington/Thal) is currently the preferred operation when the duct is dilated. The anastomosis must be at least 6 cm, and preferably >10 cm long. Most authorities advocate opening of the main pancreatic duct proximally to within 1 cm of the duodenal border thus protecting the pancreaticoduodenal vasculature. All pancreatoliths must be carefully removed prior to performing the anastomosis. It appears immaterial whether the jejunal mucosa is anastomosed in one or two layers to the pancreatic duct mucosa or to the capsule.

The literature is replete with numerous testimonials as to the efficacy of lateral pancreaticojejunostomy in providing short term pain relief[3,9,29–32]. How much of this can be attributed to placebo effect or to the fact that patients take better care of themselves in the early postoperative months is unknown. It is clear, however, that the results deteriorate with time even if the pancreaticojejunal anastomosis remains patent. Analysis of available pooled data suggests that short-term pain relief, in selected hands, is achieved in some 70–80 per cent of patients. At 5 years, <50 per cent of patients are pain free. Of note is that Sato *et al.*, from Japan, reported results which are vastly superior than anticipated, with pain relief in 90 per cent of 43 patients at 9 years[5]! Recently, Bradley reported a 66 per cent incidence of long-term pain relief with an average follow-up of 69·3 months[9]. If the patient has any cystic lesion of the pancreas, the same loop of jejunum may be used to decompress the cyst. Unless an isolated cyst is fairly large (> 5 cm) its drainage alone rarely abolishes the patient's pain.

Pancreatic resections

The rationale of partial resective procedures for chronic pancreatitis must be seriously questioned since true focal disease without a traumatic cause is exceedingly rare. Removal of 'dominant' disease is illogical since it leaves behind a remnant that is abnormal and will be progressively affected by the disease process.

The Whipple procedure. Gall from Erlangen advocates a standard pancreaticoduodenectomy of the Whipple type and reported superlative results[33,34]. It is not clear from his data whether this operation is undertaken for pain relief or for local complications within the head of the gland such as duodenal stenosis, biliary obstruction, cyst formation, or development of a focal mass. The justifications for advocating a Whipple pancreaticoduodenectomy are as follows:

1. The cellular changes in chronic pancreatitis are often dominant in the pancreatic head and the uncinate process.
2. The body and tail of the pancreas contain a greater proportion of islets.
3. Biliary or duodenal obstruction is relieved.
4. Undetectable pancreatic cancer may be found at a microscopic level and cured by the resection.

In making a decision to perform the Whipple procedure, the following disadvantages must be carefully weighed, namely increased operative risk (except in the best of hands), the functional consequences of gastric resection and a vagotomy, and the persistence or recurrence of pancreatitis in the glandular remnant. Although Gall reimplants the pancreatic remnant into the upper jejunum, he also occludes the duct remnant with aprolamine (Ethibloc) prior to performing this anastomosis. The logic behind this dual procedure is not clear and is rather reminiscent of the 'belt and braces' philosophy.

In their early experience of 49 pancreaticoduodenectomies for chronic pancreatitis Gall and his colleagues had an operative mortality of 8 per cent, a 20 per cent incidence of late death, and a 56 per cent incidence of late favourable results. The authors described an incidence of 25 per cent for recurrent pancreatitis and it was this that led them to advocate occlusion of the pancreatic duct remnant with aprolamine[33]. Their experience during the period 1978–1981 involved 116 patients with an operative mortality of 1 per cent. The results in 92 patients followed over a short period (3 months–3 years) showed some variance between the authors' assessment and the patients' evaluation[34]. The authors report that 90 per cent of patients had complete freedom from symptoms and 10 per cent had only mild discomfort. The patients admitted to a 29 per cent incidence of very good results and a 65 per cent incidence of satisfactory results. The authors emphasized that the endocrine consequences of duct occlusion are inconsequential because the pancreatic islets survive the exocrine glandular atrophy and the fibrosis.

In recent years, most surgeons who perform a Whipple procedure for benign disease advocate the pylorus preserving technique advocated by Traverso and Longmire. This preserves the motor, secretory and reservoir functions of the stomach and diminishes the risk of dumping syndrome (*see below*).

Distal resection. Distal pancreatectomy of various magnitudes, i.e. 40–95 per cent, is hard to justify except for true focal disease which is usually of traumatic origin. There is a large disparity in the reported results and the extent of the resection has different connotations to different surgeons[3,6,33–37]. The bulky uncinate process is often left behind. Post-splenectomy sepsis is a danger of unknown magnitude and the only advantage of the operation is that adjacent gastrointestinal structures are not removed. In this author's opinion such an operation has a very limited, if any, role since, in most instances, it will need to be converted into a total pancreatectomy at a later date.

The Ann Arbor experience with 'near total' or 'subtotal' (80–95 per cent) distal pancreatectomy was carefully reviewed by Frey *et al.* who reported early pain relief in over 80 per cent of patients[36]. This initial excellent result was not maintained in the long term and at a mean follow-up of 7·8 years the authors reported that 56 per cent of patients were 'alive and well'. Thus, the percentage of satisfactory results is more or less identical to that reported after more conservative distal resections or after pancreaticoduodenectomy of the Whipple type. Of great importance is the fact that the incidence of induced diabetes mellitus following such radical distal resections was 72 per cent, namely twice that reported following pancreaticoduodenectomy or more limited distal resections. The authors reported an incidence of late death of 27 per cent and this was attributed to the metabolic consequences of the extended resections. In 1981, Frey commented that the advent of endoscopic retrograde cholangiopancreatography (ERCP) has modified his approach, since he now appreciates that the disease is more frequently concentrated in the head of the gland than elsewhere[38]. He now performs more pancreaticoduodenectomies and less subtotal distal resections. To confuse the issue further, Turcotte, who is still in Michigan while Frey moved to California, remains in favour of radical distal resections and quoted 88 per cent of 'good or fair' relief of pain with an estimated 5-year survival rate of 75 per cent!

Total pancreatectomy. Extirpation of the entire gland, in theory completely removes the primary source of the initial pain. Quite understandably, there is great reluctance for the operation which is therefore relegated to a 'last resort' option. It is said to have a high operative risk, hence the patients and the surgeons must both be carefully selected. The metabolic consequences are often reported to be uncontrollable but in this author's experience this is not usually true, provided that the patients are carefully selected, rehabilitated and properly educated. The operation is often tried after all other surgical procedures have failed. Pyloric preservation as advocated by Traverso and Longmire is clearly desirable since it allows the patient to eat normal size meals and diminishes the risk of dumping syndrome[39]. Patients with a history of duodenal ulcer or a scarred duodenal bulb are clearly not candidates for this operation. It is worth reinterating that the blood supply to the stomach and first part of the duodenum is entirely dependent on the left gastric, the gastroduodenal, and the right gastric arteries. This author is aware of one situation where a highly selective vagotomy was added to the operation with disastrous consequences of gastric ischaemic necrosis.

As late as 1978, a review of the English literature by Braasch *et al.* revealed only 53 instances of total pancreatectomy for chronic pancreatitis with limited follow-up[12]. The Lahey Clinic group then reported 26 carefully selected patients treated by total pancreatectomy between 1952 and 1976. The indication for total glandular extirpation in 23 of these patients was failure of other surgical procedures and, between them, these 23 patients had had 62 prior unsuccessful operations. There was no operative mortality but 12 patients died during the period of observation which ranged from 1 to 17 years (mean 5 years). Four of these patients had good or excellent results prior to death but 7 of the 12 clearly died from metabolic complications or anastomotic ulceration. Of 14 living patients observed for 1–12 years (mean 4 years), 11 (79 per cent) felt better than they had felt before operation. Control of diabetes was fairly good for 12 patients who also had reasonable control of steatorrhea.

In a recent issue of this journal, Russell and his colleagues at the Middlesex Hospital recommended a duodenum-preserving total pancreatectomy for end-stage pancreatitis[40]. As they pointed out, this operation is not new since it is often performed in infants and children for intractable hypoglycaemia due to nesidioblastosis[41]. Fourteen patients underwent the procedure for pain as the main indication. The results are impressive with no mortality and an acceptably low morbidity. Of note is that one patient developed a biliary stricture which needed reoperation. Nine of the fourteen patients no longer require analgesics and they are all part of a regular narcotic analgesic rehabilitation programme. Only two of the fourteen patients appear to have had significant problems with diabetic control. The authors emphasized the importance of preserving total gastrointestinal continuity and the secretory and absorptive function of the duodenum, as well as the avoidance of performing intestinal and biliary anastomoses.

It is clear from this preliminary report that the operation is likely to gain acceptance into our surgical armamentarium for end-stage chronic pancreatitis. None the less, some reservations should be expressed. Careful selection of the appropriate case is essential to duplicate Russell's results. Mobilization of the uncinate process from the superior mesenteric vessels and the head of the pancreas from inside the C-loop of the duodenum is not always easy, especially if there is already evidence of peripancreatic fibrosis and biliary or duodenal obstruction. The foregut and midgut vasculature and their branches have a wide array of anatomical variations and are often involved with arteriosclerotic disease[42]. The distal common bile duct has also an unpredictable vascular supply. My bias is that the operation is not suitable for most patients. We all should be worried about leaving a duodenum that is truly 'dusky blue in colour'. Be that as it may, this operation, as well as all major pancreatic resections, should not be attempted by the occasional pancreatic surgeon who performs one or two cases every few years. Of note is that the mean age of Russell's patients was only 34 years with a range of 19–45 years. The operation is definitely not suitable for malignant disease in the head of the pancreas or periampullary region, or for patients who may have significant arteriosclerosis[43].

Operation for complications

Operating for complications of chronic pancreatitis is much more rewarding than operating for pain, especially if the complication is life threatening. It is most important that both the surgeon and the patient have a clear understanding of the fact that correction of a complication does *not* invariably provide pain relief.

Vascular complications

Vascular involvement of branches of the splenic artery, left gastric artery or gastroduodenal artery is diagnosed by angiography and massive haemorrhage can be controlled by embolization followed by urgent operation[36]. As a rule, resection of the affected segment of pancreatitis is recommended. 'Thrombosis' of the splenic, and occasionally of the portal, vein is not an infrequent complication of acute or chronic pancreatitis[44,45] The pancreatitis may be occult and painless. True 'thrombosis' of the splenic vein is not always documented after pancreatic resection, but the pancreatic and peripancreatic fibrosis clearly occludes the splenic vein over a long segment and leads to left-sided (segmental, sectorial, sinistral) portal hypertension and gastric varices. Chronic blood loss as well as massive gastric variceal bleeding have been documented in these patients. Splenectomy is curative. In the emergency situation transgastric oversewing of the actively bleeding varices may also be necessary. Howard reported two patients in whom he was forced to perform emergency total gastrectomy and splenectomy for exsanguinating haemorrhage[46]. The underlying pancreatitis should be treated on its own merits based on the clinical situation, although a concomitant distal pancreatectomy is the procedure most commonly performed. In this author's opinion, the case for either total gastrectomy or distal pancreatectomy is hard to justify in this setting.

Biliary and duodenal obstruction

Biliary and duodenal obstruction often coexist and can be relieved by appropriate bypass procedures provided that adequate biopsies have been taken to rule out, as far as possible, a concomitant cancer. As with all needle biopsies of the pancreas, there is a limit to the number of biopsies which can be taken and sampling error is the major problem[47].

Biliary obstruction. Stabile *et al.* have reviewed thoroughly the problems associated with common bile duct stricture from chronic pancreatitis[48]. Partial obstruction of the distal common bile duct often occurs because of the associated oedema and inflammatory reaction during the course of acute pancreatitis. This invariably subsides with resolution of the acute process and does not require any specific therapy unless a major complication such as a pseudocyst or abscess develops in the head of the pancreas. The question of a stone in the common bile duct must always be addressed in this situation.

With chronic pancreatitis a fixed high grade stenosis of the distal pancreatic duct is not an uncommon sequel and the clinical differential diagnoses remain cancer of the head of the pancreas, distal bile duct, or ampulla of Vater.

The obstruction is the result of progressive fibrosis in the head of the gland. Such biliary obstruction can be insidious and largely asymptomatic. Serum alkaline phosphatase elevation greater than twice the upper limits of normal which persists for longer than 1 month is a reliable indication of distal common bile duct obstruction[49]. This stricture has been demonstrated, by sequential liver biopsies, to be associated with progression from hepatic cholestasis to frank biliary cirrhosis. Less frequently, acute septic cholangitis can develop and also represents a lethal complication of common bile duct stricture due to chronic pancreatitis. The vast majority of patients with biliary stricture due to chronic pancreatitis are alcoholic[50]. One report implicates gallstones in 16 per cent of patients, but such patients were all documented to be alcoholic abusers[51]. The general recommendation is that all patients with chronic pancreatitis should undergo direct cholangiography under any of the following circumstances:

1. A persistently elevated alkaline phosphatase level, especially if it is twice the normal value.
2. Persistent jaundice.
3. An attack of documented cholangitis.

Endoscopic retrograde cholangiopancreatography has the advantage over percutaneous transhepatic cholangiography (PTC) in that it can also demonstrate any associated pancreatic ductal pathology as well as the characteristic long smooth stricture of the common bile duct with proximal biliary dilatation. The choice of operative biliary decompressive procedure generally lies between choledochoduodenostomy or choledochojejunostomy Roux-en-Y after transection of the proximal bile duct. Routine cholecystectomy is advised because of the tendency for gallbladder stasis and stone formation. Transduodenal sphincteroplasty is an inadequate operation because the distal common bile duct stricture is generally too long. Adjunctive operative procedures such as cyst or duct drainage or gastrojejunostomy with vagotomy are occasionally needed. It is clear that significant pain reduction should *not* be anticipated from biliary decompression. The therapeutic goals of biliary decompression are simply relief of jaundice and prevention of biliary cirrhosis and septic cholangitis.

Duodenal obstruction. Duodenal obstruction is also a documented complication of chronic pancreatitis. It may or may not be associated with biliary stenosis[52,53]. Careful pre-operative evaluation including ERCP is essential to exclude congenital lesions of the duodenum and pancreas and malignant disease in and around this area as well as stenosis due to duodenal ulceration. The condition must not be confused with transient oedematous duodenal compression and stasis which is a usual accompaniment of acute pancreatitis and which resolves spontaneously as the pancreatic oedema subsides.

Chronic duodenal obstruction from pancreaticoduodenal fibrosis is uniformly relieved by a gastrojejunostomy. This author routinely performs a truncal vagotomy to diminish the long-term risks of stomal ulceration.

Cancer versus *chronic pancreatitis*

Under suitable conditions patients with biliary and/or duodenal obstruction due to chronic pancreatitis are best treated by pancreaticoduodenectomy of the Whipple type, especially if pain is a significant part of the clinical picture. Suspicion, or fear, of an incidental cancer is becoming a more frequent indication for pancreatic or pancreaticoduodenal resection in recent years for several reasons[46,54]. White and Slavotinek have reported performing pancreaticojejunostomy for drainage of chronic pancreatitis in nine patients who died of pancreatic cancer a few months later[26]. Several other surgeons have admitted, or reported similar unfortunate experiences. Gall and his colleagues recalled that suspicion of carcinoma was the most significant factor in their decision to perform pancreaticoduodenectomy in 20 of their 68 patients with chronic pancreatitis[33,34]. Pancreatic biopsy of an indurated, enlarged and chronically inflamed head of pancreas is fraught with a high incidence of sampling error and cannot be relied upon to exclude totally a small concomitant cancer[47]. Of the 16 small cancers resected by Moossa and Levin, 4 were incidentally found by microscopic examination of the specimen resected with a presumptive diagnosis of chronic pancreatitis[55]. Clearly, the decision to resect such a gland has to be made on careful assessment of the clinical situation and the cost/benefit ratio in each individual patient.

Pancreatic cysts and pancreatic ascites in chronic pancreatitis

Cyst formation is not uncommon in chronic pancreatitis. The majority of these cysts are not pseudocysts and they often are intrapancreatic in location. Whether these cysts are true retention cysts, are the result of duct ectasias, or are pseudocysts, is purely a matter of nomenclature and their management follows the same guidelines. Unless a cyst is fairly large (>5 cm in diameter) or has developed a complication (such as vascular involvement, infection, rupture), internal or external drainage, or pancreatic resection should be approached with caution. Thus, the management of pancreatic cysts has to be planned in conjunction with an operative strategy to relieve the patient's symptoms. The random, internal or external, percutaneous or operative, drainage of a cyst rarely if ever relieves the patient's pain.

Spontaneous rupture of a main pancreatic duct or of a cyst wall leading to non-catastrophic leak of pancreatic juice into the peritoneal cavity is the underlying abnormality leading to the clinical entity of pancreatic ascites. Any alcoholic with ascites and reasonable normal liver function should be suspected of having this condition. Most cases are associated with alcoholism; a few follow pancreatic trauma. The onset may be abrupt or insidious. Approximately 15 per cent of the cases have an associated pleural effusion and chest symptoms may be prominent. A history of pancreatitis may be absent and the ascites may be wrongly assumed to be of the common hepatic variety. A high amylase and high protein content of the ascitic fluid is pathognomonic of the condition.

The optimal treatment of pancreatic ascites is controversial. SarKaran and Walt[56] recommended early operation in all cases. Zuidema and Cameron[57] advocated an initial trial of conservative therapy consisting of repeated paracentesis, nasogastric suction and intravenous nutrition. If this regimen fails in 2–3 weeks, then operation becomes essential.

Pre-operative ERCP is essential in the planning of a surgical strategy. The two surgical options are partial pancreatectomy with cyst excision and internal drainage of the cyst or the ruptured duct. Once again, treatment has to be individualized as dictated by the ductal anatomy demonstrated by pancreatography and by the laparotomy findings.

Discussion

The undeniable reality is that chronic pancreatitis is not primarily a surgical disease and only becomes so when a surgically correctable complication develops. Thus, the benefits and limitations of surgical intervention, especially if operation is undertaken for pain relief, must be clearly understood. Each patient must be treated carefully on an individual basis and the reasons for choosing a particular procedure must be well delineated. Finally, the results of surgical treatment must be properly analysed and reported[58].

Since the metabolic consequences of major pancreatic extirpation militate against its widespread use for pain control, attention is being paid in several centres to the adjunctive use of pancreatic autotransplantation in chronic pancreatitis. Early experience with islet cell infusion into the portal vein has not been encouraging[59,60]. The tough fibrous nature of the human pancreas makes it virtually impossible to obtain significant numbers of isolated islets intact. Although there have been reports of temporary reduction in insulin requirement after such transplantation, current opinion is that no recipient has become insulin independent. In addition, catastrophic and fatal complications have been reported and include acute portal hypertension and disseminated intravascular coagulation.

Segmental or whole organ pancreatic autotransplant has been tried following total or near total pancreatectomy in a small number of cases. The resected gland is usually transplanted into the groin or into the pelvis. The ducts are usually injected with neoprene and ligated. Tosatti *et al.* reported three such patients, followed for approximately 1 year, to be free of pain and of diabetes mellitus[61]. Rossi *et al.* have also reported three patients followed for 2–18 months with similar encouraging outcomes[62]. If these results are confirmed, it may well dictate that pancreatic resection will be performed at an earlier stage in the course of chronic pancreatitis before islet destruction has become too extensive.

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Neural control of internal anal sphincter function

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The effect on anal tone of electrical stimulation of the presacr (hypogastric) sympathetic nerves has been studied in eight patien during abdominal rectopexy or restorative proctocolectomy. A sharp fa in anal pressure occurred in seven patients (mean fall 59 cmH_2O; rang 35–80 cmH_2O). In one patient given a β- and α-sympatheti blocking drug (labetalol 200 mg) intra-operatively, the anal pressur decreased by 15 cmH_2O. These observations show that stimulation o the presacral sympathetic nerves causes relaxation of the internal an sphincter and implies that these nerves may induce relaxation of th sphincter in vivo. *The pathway of the recto-anal reflex has been studie intra-operatively in three patients undergoing rectal excision. The recto anal reflex is present after presacral nerve blockade and after fu mobilization of the rectum, but is abolished by circumferential recta myotomy. The reflex has a local intramural pathway. This observatio validates the assumption that absence of this reflex is a feature o aganglionosis, as in Hirschsprung's disease.*

Keywords: Anal sphincter, electromyography, rectum

Over the past 10 years much has been learned about the function of the striated external anal sphincter and pelvic floor particularly through the study of patients with faecal incontinence[1–7]. In contrast much less is known about internal anal sphincter (IAS) function, particularly its neurogenic control. We have investigated the neural control of the IAS by intra-operative stimulation of the presacral (sympathetic) nerves. We have also investigated the neural pathways of the recto-anal reflex.

The resting anal pressure is largely produced by tonic contraction of the IAS[8,9]. The IAS is innervated by sympathetic nerves via the hypogastric (presacral) nerves derived from the fifth lumbar segment[10]. Its parasympathetic innervation is derived from the sacral outflow via the pelvic plexus. It also receives innervation from the enteric nervous system, consisting of non-cholinergic, non-catecholaminergic nerves, which may utilize purinergic or peptidergic transmitters[11,12]. Stimulation of the presacral nerves in man and animals has been reported to produce both contraction and relaxation of the IAS[13–17]. We have examined this question by studying the effect of intra-operative presacral nerve stimulation on anal canal pressure.

The recto-anal reflex, described by Gowers (1877)[18] and Denny-Brown and Robertson (1935)[19] consists of IAS relaxation in response to distension of the rectum. The reflex is absent in Hirschsprung's disease; much interest has centred on this because of its diagnostic role both in children and adults[20]. We have investigated the neural pathways of the recto-anal reflex by intra-operative study.

Patients and methods

The investigations were performed with the consent of the Combined Ethical Committee of St. Bartholomew's and St. Mark's Hospitals, and with each patient's informed consent. Eight consecutive patients were studied. Two patients underwent abdominal rectopexy for rectal prolapse, and six had restorative proctocolectomy for chronic ulcerative colitis. There were four men and four women, aged 18–48 years (mean 33 years). In each patient the surgical procedure was carried out using general anaesthesia and lorazepam premedication. No patient received anticholinergic agents with the premedication or during anaesthesia.

Presacral nerve stimulation

The presacral nerves were identified near the sacral promontory during the routine operative dissection, and held with nylon tapes. Square-wave electrical stimuli were delivered in turn to the right and left nerves using a bipolar stimulator and changes in anal pressure were recorded. Trains of stimuli of variable duration (0·1–0·5 ms), rate (1–50 Hz) and intensity (10–150 V) were tested. The optimal stimulus parameters were 0·5 ms, 20 Hz, 50 V. The anal canal pressure was measured using a closed water-filled system with a microballoon 4 mm in diameter, attached by a non-distensible polyethylene tube of 2 mm outside diameter to a transducer and DC amplifier with a paper print-out (Devices MX 4-73)[21]. The probe was placed to record the maximal anal pressure and temporarily sutured in place. In four subjects simultaneous recording of rectal pressure was made using a 4 mm microballoon placed in the rectum about 10 cm from the anal verge.

The right and left nerves were then blocked by local infiltration of 0·5 per cent bupivacaine. Each nerve was stimulated proximal and distal to the site of nerve blockade while simultaneously recording anal pressure.

Recto-anal reflex

The recto-anal reflex was studied in three of the patients undergoing restorative proctocolectomy. Four experiments were carried out in each of the three patients. A soft latex rubber balloon 5 cm in length attached to a stiff polyethylene tube 3 mm in external diameter was positioned in the lower rectum. The recto-anal reflex was then tested by distension of the rectal balloon with 50 ml air. This induced a sharp fall in anal pressure after a few seconds delay.

The recto-anal reflex was retested after three operative manoeuvres: bilateral presacral nerve blockade, mobilization of the rectum by close rectal dissection, and circumferential myotomy of the rectal wall between the level of the rectal and anal balloons. The right and left presacral nerves were blocked by local infiltration of 0·5 per cent bupivacaine. The completeness of blockade was checked by stimulation of the nerve on each side as described above proximal and distal to the block, while simultaneously recording anal pressure. The recto-anal reflex was then retested.

The rectum was then mobilized, with the dissection carried out close to the rectal wall and mobilization was carried down to the pelvic floor, thereby dividing all blood vessels and extrinsic nerves supplying the rectum. The recto-anal reflex was again tested.

Circumferential myotomy of the rectum down to the submucosal layer was then carried out and the recto-anal reflex tested again with the rectal balloon positioned above the myotomy.

Results

Using 50 V, 0·5 ms, 20 Hz stimulus trains, a reproducible fall in anal canal pressure was observed in each of the eight patients. Stimuli of less than 20 V or 10 Hz or 0·5 ms did not produce a

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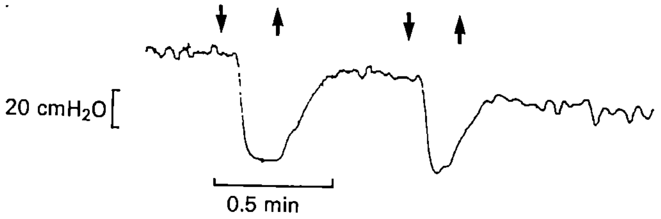

Figure 1 *Decrease in anal pressure with presacral nerve stimulation. Arrows indicate onset ↓ and end ↑ of stimulation. Baseline = zero pressure*

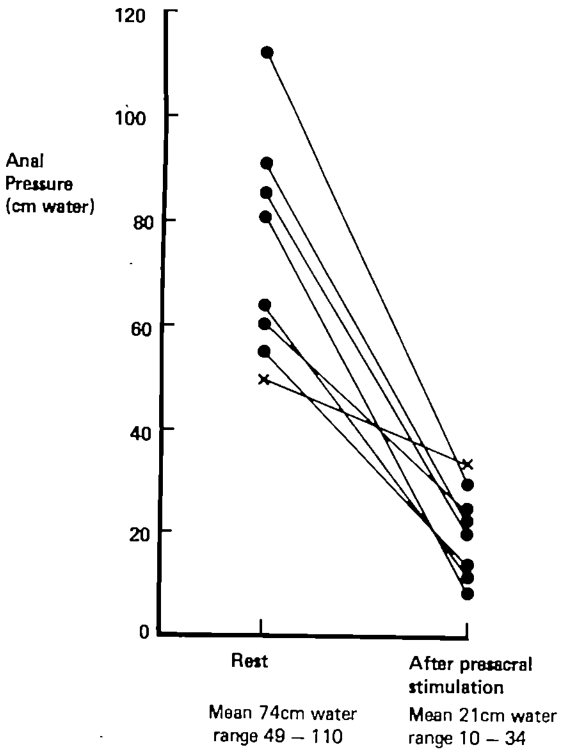

Figure 2 *Anal pressure measurements before and during unilateral presacral nerve stimulation in the eight patients. Presacral nerve stimulation caused a fall in anal pressure in each patient. The mean decrease in anal pressure in seven patients was 59 (range 35–80) cmH$_2$O. In the eighth patient (×) labetalol had been given; there was a less marked reduction in anal pressure in this patient (15 cmH$_2$O)*

reproducible response. In seven patients a sharp fall in pressure (mean 59 cmH$_2$O; range 35–80 cmH$_2$O) occurred within 2–3 s after the onset of the stimulation (*Figures 1* and *2*). In the eighth patient who was given a β- and α-sympathetic blocking drug (labetalol 200 mg) intra-operatively for hypertension prior to the recording, presacral nerve stimulation resulted in a fall in pressure of 15 cmH$_2$O. Electrical stimulation was stopped in each patient after maximal pressure fall had occurred and this resulted in a rapid return of anal pressure to the baseline resting pressure (*Figure 1*). When stimulation was prolonged for longer than about 30 s there was a slow recovery of anal pressure but to a lower level than the starting pressure. No change in rectal pressure was observed in any patient following presacral nerve stimulation. Local infiltration of bupivacaine did not have any effect on resting anal canal pressure. After local infiltration stimulation of each nerve distal to the nerve blockade produced a fall in anal pressure, while stimulation proximal to the blockade resulted in no change in pressure (*Figure 3*).

The recto-anal reflex was clearly demonstrated in each of the subjects tested, prior to the three experimental conditions. The reflex was unchanged after bilateral presacral nerve blockade (*Figure 3*) and also after full rectal mobilization. In each subject, however, it was completely abolished by circumferential rectal myotomy.

Discussion

Previous reports of electrical stimulation of the presacral nerves in man and animals have reported inconsistent effects. Rankin and Learmonth[13], in a single patient reported IAS contraction. However, no pressure recording was made and the sphincter response was judged only by digital examination. Carlstedt *et al.*[14] demonstrated transient IAS relaxation followed by contraction in 13 of 15 cases. An excitatory effect of sympathetic stimulation was inferred by Frenckner and Ihre[22] in a study of IAS tone during spinal anaesthesia at high and low thoracolumbar levels. Contraction of the IAS with sympathetic stimulation has also been reported in cats[15] and dogs[16]. Shepherd and Wright[17] reported IAS relaxation after sympathetic stimulation; 11 of the 14 patients studied had Hirschsprung's disease or acquired megacolon.

We have shown that presacral nerve stimulation invariably causes IAS relaxation. Our finding that high frequency stimulation is required to obtain reproducible IAS relaxation may explain the conflicting reports in the literature, where the precise stimulus parameters were not always described. Shepherd and Wright[17] who observed IAS relaxation in all patients studied used similar stimulus parameters to those used by us.

Sphincter relaxation due to stimulation distal but not proximal to the point of nerve blockade confirms that the response is due to efferent sympathetic stimulation. In addition to this *in vivo* adrenergic relaxation of the IAS, relaxation of the human IAS also occurs *in vitro* as a response to stimulation of the non-cholinergic, non-adrenergic innervation of this muscle[11]. Experiments on isolated human IAS muscle strips have shown that noradrenaline causes contraction, adrenaline has a variable effect and isoprenaline induces relaxation. Relaxation of the IAS induced by sympathetic nervous activity is probably due to excitation of β-adrenoreceptors since α-adrenoreceptor antagonists convert noradrenergic contraction of IAS muscle strips into relaxation[23,24]. In human volunteers β-adrenergic relaxation of the IAS was confirmed by infusion experiments with isoprenaline, an effect that could be blocked by propranolol[25].

At rest the IAS is in a state of tonic partial contraction, shown by a zone of pressure (60–100 cmH$_2$O) in the anal canal[8,9]; distension of the rectum induces relaxation of the IAS[18–20]. Duthie and Bennett[26] suggested that the role of this recto-anal relaxation reflex may be to allow rectal contents to come into contact with the sensory epithelium of the anal canal, allowing 'sampling' of rectal contents as an aid to continence. Anal sampling may also be important in discriminating between flatus and faeces[27].

The recto-anal reflex is absent in Hirschsprung's disease, in which intramural ganglia are absent over a variable length of rectum and colon[20]. The reflex has been shown to be independent of centres above the level of the spinal cord as it is present after spinal cord transection[28]. Denny-Brown and

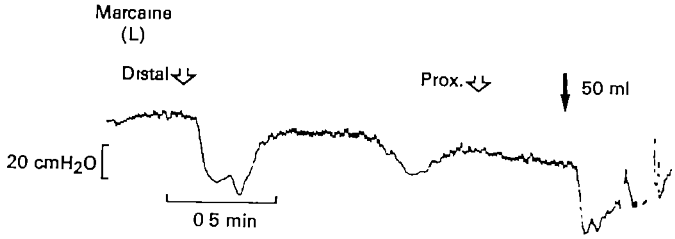

Figure 3 *Stimulation of the left presacral nerve, distal and proximal (open arrows) to the bupivacaine nerve block demonstrates absence of anal pressure fall after stimulation proximal to the block. At the closed arrow 50 ml air was used to distend a rectal balloon; the recto-anal reflex was present despite bilateral presacral nerve blockade. Baseline = zero pressure*

Robertson[19] postulated from the delayed time course of the reflex that it was intramural. We have shown that the reflex is present after bilateral hypogastric nerve blockade and after complete isolation of the rectum from its extrinsic nerve supply. These observations, together with absence of the reflex when the rectum is distended oral to a circumferential myotomy, confirms that the pathways for this reflex are entirely within the wall of the rectum and anal canal.

The recto-anal reflex is usually absent after proctectomy and colo-anal anastomosis but returns in some patients after 1–3 years[29], perhaps following regeneration of intramural enteric nerves across the anastomosis. We have found that the recto-anal reflex can also be elicited in some patients after ileo-anal anastomosis, suggesting that enteric nerves also regenerate across this anastomosis.

Enteric inhibitory nerves are involved in peristalsis throughout the gut, causing a wave of inhibition running ahead of material travelling through the gut, thus allowing accommodation and distension to the descending bolus in the pharynx, stomach, small intestine and colon[30]. The IAS, representing a specialized portion of the circular smooth muscle fibres of the gut, should thus be innervated by enteric inhibitory neurones of similar type to those in more oral parts of the gut. These enteric inhibitory neurones are probably purinergic or peptidergic[11,12,31]. Penninckx and Mebis[32] showed that adrenergic nerves were not involved in the recto-anal reflex, a finding supported by our experience of preservation of the reflex after bilateral hypogastric nerve blockade. Our finding that the recto-anal reflex is a local reflex within the wall of the anorectum is in keeping with the principle of local enteric nerve inhibition.

We have therefore shown that the IAS has an extrinsic inhibitory sympathetic nerve control, which can function independently of the intrinsic nerve control mediated locally as the recto-anal relaxation reflex.

Acknowledgements

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Results of proctocolectomy for Crohn's disease

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Seventy-four patients have had a one-stage proctocolectomy for the management of Crohn's disease. Indications for operation were: acute colitis 28 per cent, chronic colitis 39 per cent, perianal disease 13 per cent, proctitis and perianal disease 8 per cent, bleeding 5 per cent, coexisting colonic malignancy 7 per cent. There were two hospital deaths (2·7 per cent), both associated with sepsis. Late deaths ($n=13$) were most commonly associated with reoperations for recurrent disease ($n=3$), cardiovascular disease ($n=4$) and colorectal carcinoma ($n=1$). Postoperative complications were principally associated with sepsis. Cumulative reoperation rates at 5 and 10 years were 19 and 24 per cent respectively. Recurrence was unrelated to the age of the patients, the duration of disease, or the presence of ileal disease at the time of colectomy.

Keywords: Ileostomy, proctocolectomy, Crohn's disease, mortality and morbidity, recurrence rates

Surgical management of Crohn's disease of the colon is often by colectomy and ileorectal anastomosis. This restores patients to good health and avoids a permanent stoma, but there is concern about the incidence of recurrence after this operation[1–10]. The alternative procedure of colectomy and ileostomy is less attractive for the patient but if there is serious anorectal disease, construction of a stoma and resection of the colon may be the best surgical option; furthermore, there is some evidence to suggest that recurrence rates are lower after this procedure[3,4,6,8].

This paper reports the indications for, and results of, surgery in 74 patients having a proctocolectomy for Crohn's colitis. The incidence of recurrent disease and factors which might affect recurrence are discussed.

Patients and methods

Seventy-four patients (30 men, 44 women) have been treated by one-stage proctocolectomy for Crohn's colitis between 1956 and 1984. This represents 10 per cent of all cases of Crohn's disease followed up in this unit between 1956 and 1984.

The median age at diagnosis was 25 years (range 9–64 years). The diagnosis was made by pre-operative histology in 53 per cent[11,12] and has subsequently been confirmed from the colectomy specimen in all patients. The median time from diagnosis to colectomy was 4·1 years (range 0–33 years). The median age at colectomy was 32 years (range 14–67 years).

Thirty-six patients had had no previous surgery; five patients had had a perianal abscess drained. Early in the series, 10 patients had had a defunctioning ileostomy before proctocolectomy. There were 23 patients who had previously undergone 39 operative procedures for Crohn's disease before large bowel resection was carried out. The procedures were ileal resection in 12 patients, ileocaecal resection in 8 patients, bypass of ileocaecal disease in 2 patients, segmental colonic resection in 10 patients, colostomy for perianal sepsis in one patient, appendicectomy in 4 patients, excision of a fistula-in-ano in one patient and dilatation of a rectal stricture in one patient.

The current status of all patients was assessed to 30 June 1984 following clinical examination by the authors ($n=51$), by letter ($n=8$), or by reference to notes in those who had died ($n=15$).

The cumulative recurrence rates of two parameters have been calculated: (i) patients undergoing a resection for histologically proven recurrent disease (cumulative reoperation rate); (ii) patients in group (i) plus those having radiological or endoscopic evidence of recurrent disease (cumulative recurrence rate).

The method of calculating the cumulative recurrence and reoperation rates is that described by Berkson and Gage[13] and summarized by Greenstein and his colleagues[9].

The results were calculated for the whole review period 1956–1984, and also for the first half (1956–1969) and second half (1970–1984) of the 28-year period.

Results

Common indications for proctocolectomy were general ill health and diarrhoea in 29 patients, and acute colitis in 21 patients. Ten patients had severe perianal disease, six had severe proctitis with perianal disease, three required a colectomy for haemorrhage, and a further five for malignancy or severe dysplasia.

The principal sites of disease were total colitis in 47 patients, segmental colitis in 11 patients and severe anorectal disease in 16. Twenty-one patients had distal ileal disease in addition to colitis. Eight patients had extra-intestinal manifestations of Crohn's disease (arthritis in one patient, cirrhosis in two patients, erythema nodosum in two patients, pyoderma gangrenosum in one patient, iritis in one patient and retroperitoneal fibrosis resulting in ureteric obstruction in one patient).

Severe rectal involvement as assessed by radiology or sigmoidoscopy was present in 58 patients, 3 of whom had a rectal stricture. Severe perianal disease was present in 16 patients, 3 of whom had a perianal abscess at the time of colectomy. Twenty-eight patients had a pre-operative fistula (twenty-two a fistula-in-ano, five a rectovaginal fistula, and one an ileorectal fistula).

Perioperative antimicrobial prophylaxis was used in 29 patients (39 per cent) only, (4 patients in the first half of the review period and 25 patients in the second half). Thirty-six patients (49 per cent) received perioperative steroid cover (14 patients in the first half of the review period, 22 patients in the second half).

Postoperative morbidity and mortality

There were two deaths within 31 days of operation giving an operative mortality of 2·7 per cent. One death occurred in 1981 secondary to intra-abdominal sepsis, the other in 1960 secondary to bronchopneumonia. The principal postoperative complications were wound sepsis (8 per cent), infection in the perineal wound (22 per cent) and intra-abdominal abscess (9 per cent). The incidence of these complications did not differ when the first 14 years of the review were compared with the most recent 14 years (*Table 1*).

The overall mean postoperative stay was 31 days (range 9 days to 4 months).

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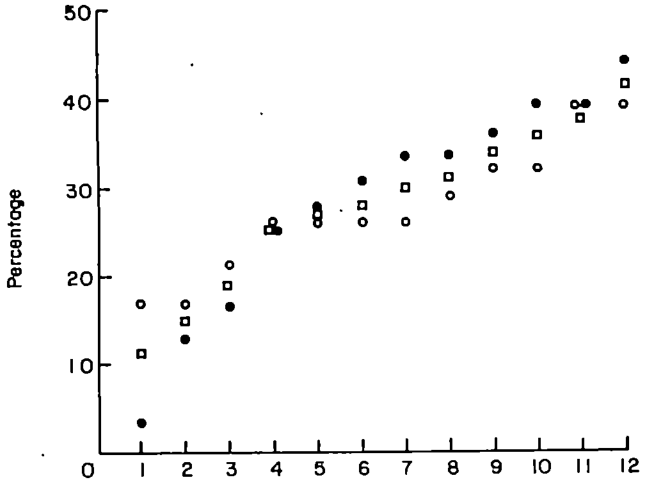
Table 1 *Postoperative complications*

	Number of patients		
	1956–1969 (n=32)	1970–1984 (n=42)	1956–1984 (n=74)
Abdominal wound sepsis	3 (9)	3 (7)	6 (8)
Perineal wound sepsis	6 (19)	10 (24)	16 (22)
Intra-abdominal abscess	4 (12)	3 (7)	7 (9)
Septicaemia	1 (3)	—	1 (1)
Serious bleeding	3 (9)	2 (5)	5 (7)
Pneumonia	1 (3)	1 (2)	2 (3)
Deep vein thrombosis	—	2 (5)	2 (3)

Values in parentheses are percentages



Whole group (□)												
No. recurrence	8	3	3	5	1	1	1	1	2	1	1	2
No. at risk	70	69	65	62	58	55	53	51	49	40	35	34
1956-1969 (●)												
No. recurrence	1	3	1	3	1	1	1	0	1	1	0	2
No. at risk	29	29	29	28	28	27	26	25	25	25	25	25
1970-1984 (o)												
No. recurrence	7	0	2	2	0	0	0	1	1	0	1	0
No. at risk	41	40	36	34	30	28	27	26	24	15	10	9

Figure 1 *Cumulative ileal recurrence rates for whole group and for those having operations in the years 1956–1969 and 1970–1984*

There were 13 late deaths. Eight occurred after further surgical treatment: three were associated with recurrent Crohn's disease one from colorectal carcinoma, two from other malignancies (maxillary and thymic tumour), one following elective surgery and one from septicaemia following renal transplantation. There were four cardiovascular deaths and one suicide.

The mean duration of follow-up since proctocolectomy was 12·1 years. During this time 55 (76 per cent) of the 72 patients followed have required readmission. The major reasons for readmission were surgical recurrence (41), recurrence treated medically (6), elective surgery (13), ileostomy flux (22), adhesive obstruction (11) and ileostomy refashioning without evidence of recurrence (8).

Recurrence rates

Follow-up ranged from 6 months to 36 years (mean: 12·1 years) after surgery. Four patients have been lost to follow-up.

Twenty-four patients (33 per cent) had a total of 41 recurrences requiring reoperation for histologically proven Crohn's disease. Twelve patients had only one recurrence: eleven in the terminal ileum or ileostomy and one in the duodenum. The remaining 12 patients had more than one recurrence: 8 patients had two ileal recurrences, 2 patients had three ileal recurrences, 1 patient originally had a jejunal recurrence followed by 3 ileal recurrences, while a further patient had an ileal recurrence followed by 2 recurrences in a perineal sinus.

Fourteen patients have had twenty-one radiological recurrences treated medically, but nine of these patients have eventually required reoperation. Eighteen recurrences occurred in the distal ileum or ileostomy, one in the jejunum, one in the duodenum and one in a perineal sinus.

Ileal recurrence rates

The majority (89 per cent) of recurrences occurred at the ileostomy or within 25 cm of the stoma.

The mean interval from proctocolectomy to the first identification of recurrent disease was 5·8 years (range 0·2–17·3 years). The results are shown in *Table 2* and graphically in *Figures 1* and *2*.

Factors affecting reoperation rates

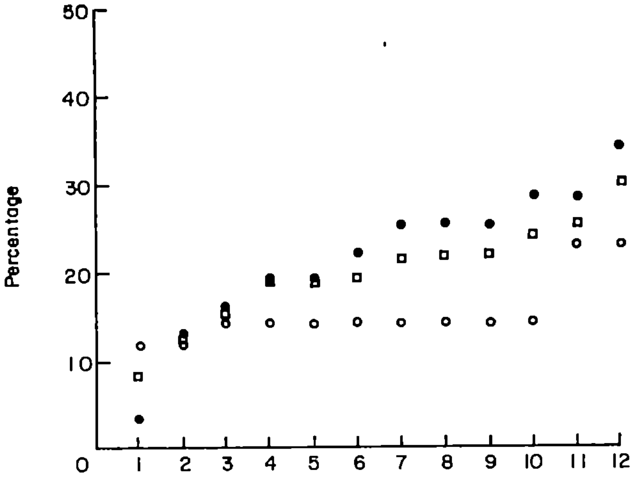
Age at proctocolectomy. The cumulative reoperation rate calculated for patients who were less than 30 years old at the time of their proctocolectomy was 21 per cent at 10 years, which did not differ significantly from the reoperation rate for the overall group (24 per cent).

Duration of disease before colectomy. The cumulative reoperation rate at 10 years for patients undergoing

Table 2 *Cumulative percentage reoperation and recurrence rates after 10 years of follow-up*

	Reoperation	Recurrence
Complete time period (1955–1984)	24%	35%
First half (1955–1969)	28%	39%
Second half (1970–1984)	15%*	32%

* $P<0.05$



Whole group (□)												
No. reop.	6	3	2	2	0	1	1	0	0	1	1	2
No. at risk	70	69	65	62	58	55	53	51	49	40	35	34
1956-1969 (●)												
No. reop.	1	3	1	1	0	1	1	0	0	1	0	2
No. at risk	29	29	29	28	28	17	16	25	25	25	25	25
1970-1984 (o)												
No. reop.	5	0	1	1	0	0	0	0	0	0	1	0
No. at risk	41	40	36	34	30	28	27	26	24	15	10	9

Figure 2 *Cumulative ileal reoperation rates for whole group and for those having operations in the years 1956–1969 and 1970–1984*

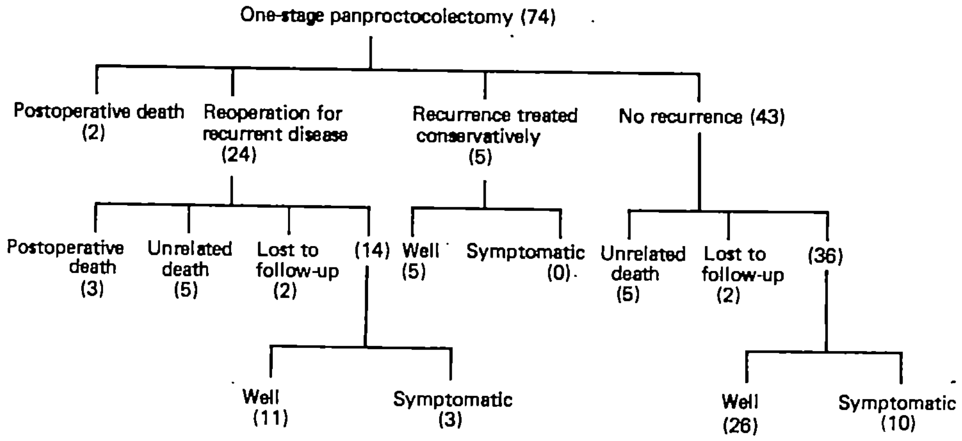


Figure 3 *Outcome of one-stage panprotocolectomy for Crohn's disease*

proctocolectomy within 5 years of diagnosis was 29 per cent which did not differ significantly from the group as a whole (24 per cent).

Initial ileal involvement

The presence of ileal disease at the time of proctocolectomy had no apparent effect on the ileal recurrence rates. The ileum was involved in 28 patients and the affected segment was resected in 22 patients, 6 of whom (27 per cent) developed an ileal recurrence requiring reoperation. Of the 6 patients in whom the diseased ileum was left *in situ*, 2 (33 per cent) developed an ileal recurrence requiring reoperation. The ileum was microscopically and macroscopically uninvolved in 46 patients and 34 per cent (16 patients) required an ileal resection for recurrence.

Current status

Fifty-five of the original seventy-four patients are still alive while the four lost to follow-up were asymptomatic when last seen. Forty-two of the surviving fifty-five patients (76 per cent) are in good health, including eleven of the remaining fourteen patients who required a further resection for recurrent disease. The details are shown in *Figure 3*.

Discussion

Although colectomy and ileorectal anastomosis may be advised if there is rectal sparing, absence of perianal disease and minimal small bowel involvement, restorative resection seems to carry a higher risk of recurrent disease than proctocolectomy[3,4,6,8,14]. Several authors have also reported a low incidence of small bowel recurrence following proctocolectomy[3,4,6,8] and we have recently shown that ileal recurrence rates after proctocolectomy are significantly less than those following colectomy and ileorectal anastomosis[15].

In this series the principal indication for proctocolectomy was general ill health and diarrhoea or acute colitis. By contrast, perianal disease was a rather uncommon indication[16]. Severe rectal disease was present in 82 per cent of the patients undergoing a one-stage proctocolectomy, which is much higher than the incidence of proctitis in patients undergoing an ileorectal anastomosis (42 per cent in our series)[14].

The operative mortality rate of 2·7 per cent is similar to other reported series[3,4,6,7] but the deaths were associated with sepsis[17]. Sepsis was also the most frequent postoperative complication and we now believe that 5-day antibiotic prophylaxis will minimize this risk[18]. However, despite this, we have not found a lower incidence of sepsis during the last 12 years when antibiotic prophylaxis has become routine. Patients undergoing proctocolectomy had a longer mean postoperative stay (31 days) compared with patients undergoing an ileorectal anastomosis (20 days)[14] but this was largely attributed to patients having to learn to care for their stoma and delay in healing of the perineal wound[19].

The majority (89 per cent) of cases of recurrent disease occurred in the distal ileum within 25 cm of the stoma which is similar to the experience of others[3,4,6,8,20]. It has been suggested that the presence of ileal involvement at the initial operation results in an increased recurrence rate[7], but in our experience this was not the case. Heuman *et al.*[21] found that the presence of disease at the margin of resection had no influence on the recurrence rates, a finding that has also been confirmed by others[5,6,10].

Usually, recurrent ileal disease does not pose a major management problem, and we were surprised to find that three deaths occurred in 24 patients requiring reoperation for recurrence.

The use of cumulative recurrence rates corrects for variable lengths of follow-up between patients and allows comparison with other series. The cumulative recurrence rate at 5 and 10 years in this series was 24 per cent and 35 per cent. Reported series vary widely with the highest reoperation rate of 89 per cent given by Greenstein *et al.*[9]. The variations are not surprising and probably occur because of different histological criteria, indications for reoperation, length of follow-up and site of original disease. Like Vender *et al.*[10], we found a slightly higher incidence of recurrence in patients undergoing colectomy within 5 years of diagnosis. During the last 14 years of follow-up, recurrences have been managed conservatively more often than in the first half of the follow-up period (reoperation rates 15 per cent at 10 years *versus* 32 per cent, while the overall recurrence rates have remained the same, 32 per cent *versus* 39 per cent).

Although some patients with Crohn's colitis manage without an operation[22], the majority eventually require surgical excision of severe disease. The decision as to which operation to perform depends on the extent and site of disease, the presence of perianal disease, distensibility of the rectum, age and attitude of the patient and their acceptance or otherwise of a stoma. A colectomy and ileorectal anastomosis often restores young patients to good health without the risk of impaired sexual function from pelvic dissection and a permanent stoma is avoided. However, proctocolectomy carries a better long-term prognosis since recurrence rates compared with ileorectal anastomosis are significantly lower[15]; furthermore, the risk of sexual impairment is now much lower since the introduction of perimuscular excision of the rectum[23].

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Announcement

Association of Surgeons in Training

Annual General Meeting

The Annual General Meeting of the Association of Surgeons in Training will be held in Liverpool from Wednesday 2 to Friday 4 September 1987. The meeting is open to all Members of the Association including those registrars whose membership has been ratified by council.

Details of the meeting can be obtained from: the local organizer, Linda de Cossart, 8 School Lane, Bidstone Village, Merseyside L43 7RG, UK; or the Secretary, Simon Ambrose, Department of Surgery, Clinical Teaching Block, General Hospital, Birmingham B4 6NH, UK.

Membership

Membership of the ASIT is open to all Senior Registrars holding accredited posts in general surgery, urology, paediatric surgery, plastic surgery, neurosurgery and cardiothoracic surgery. The Association represents the view of members on all matters relevant to senior registrars' training, besides having scientific and social functions.

If you are not a member please contact the Secretary, Simon Ambrose (address above) for details of local representatives and forthcoming meetings.

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Unaltered risk of colorectal cancer within 14–17 years of cholecystectomy: updating of a population-based cohort study

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The incidence of colorectal cancer after cholecystectomy was analysed in a historical population-based cohort study comprising 16 439 patients who were completely followed up for 14–17 years after operation. The observed number of colorectal cancers (150) was lower than the expected number of 166·3 (relative risk (RR) = 0·90: 95 per cent confidence limits 0·77–1·05) and the overall risk for colon cancer (RR = 0·95) did not differ significantly from that of rectal cancer (RR = 0·82). Separate analyses by sex, age at operation and duration of follow-up revealed relative risks close to or lower than unity. Some deviations indicating a substantially reduced risk might have been due to the play of chance alone. Our results contradict the idea both of a causal and of a non-causal association—through common aetiological factors—between surgically confirmed gallbladder disease and colorectal cancer.

Keywords: Cholecystectomy, gallbladder disease, colorectal cancer

A possible relationship between cholecystectomy and a subsequent risk of developing cancer of the large bowel has been widely discussed in recent years. The essence of the underlying hypothesis has been that elimination of gallbladder function leads to an increased intestinal load of secondary bile acids and their degradation products, with a resulting carcinogenic effect on the large bowel mucosa. This hypothesis gained considerable support both from experimental findings and from metabolic epidemiological. studies[1]. Ultimate proof of the validity of the hypothesis in terms of analytical epidemiological data linking cholecystectomy to an increased risk has been largely lacking, with the findings being incomplete and partly contradictory[1].

Therefore, a population-based historically prospective study has been undertaken in a cohort comprising more than 16 000 patients who have had a cholecystectomy. Our initial data provided no support whatsoever for the concept of an increased risk or altered distribution of colonic cancer among patients with surgically confirmed gallbladder disease. They indicated a slightly decreased risk of rectal cancer in the cohort under study, although this unexpected finding was considered preliminary and in need of further confirmation[1].

Since the completion of this initial analysis 4 years ago, the debate has continued and knowledge in this field has advanced further. Thus, the importance of environmental factors in the aetiology of large bowel cancer is generally recognized[2] and previous findings[3–6] suggesting that faecal secondary bile acids play a causal role have gained some further support[7–8]. According to one report[9] an increased proportion of secondary bile acids is an inherent characteristic of patients with gallstone disease which is unaffected by surgical removal, even of a functioning gallbladder. This observation requires modification of the hypothesis from a causal to a non-causal association between cholecystectomy and the risk of large bowel cancer. In our previous analysis the risk was related to the duration of observation after cholecystectomy. If the modified hypothesis holds true, a trend related to age—and thereby to the duration of exposure to a high proportion of secondary bile acids and their bacterial degradation products—should rather be expected.

The continuing controversy[10–19] prompted an update of our previous cohort study[1]. Important aims, in addition to that of adding three more years of observation, were to analyse separately possible trends related to age at cholecystectomy, to take advantage of methodological refinements and to further assess whether the decreased risk of rectal cancer might be due to chance alone or is further corroborated by a persistent trend.

Patients and methods

The cohort

A population-based cohort study was compiled on the basis of virtually all persons undergoing cholecystectomy in a strictly defined geographical area—the Uppsala Health Care Region—during a 4-year period from 1964 to 1967. This Region, with more than one-sixth of the entire Swedish population, is considered representative for the whole country with respect to health care facilities, incidence of large bowel cancer and distribution of urban and rural areas. The cohort was recruited from a computerized registry covering all instances of inpatient health care in that region. The registry is held by the Swedish Board of Health and Welfare and includes the national registration number (NRN) of the patient (which permits exclusive identification) and information concerning the hospital, diagnostic codes according to the international classification of diseases (ICD code) and codes referring to surgical procedures. A sample survey of hospital records indicated that the registry data had high validity[1].

As previously described in detail[1], the criterion for inclusion in the cohort was the diagnostic code indicating benign gallbladder disease in combination with a cholecystectomy with or without exploration of the common bile duct. Only appendectomy was accepted as a concomitant procedure. This basic criterion was met by 17 735 patients, 962 (5·4 per cent) of whom had to be excluded because of incomplete registration which prevented computerized follow-up. Our previous findings were thus based on 16 773 cholecystectomized patients. In the present analysis we were able to identify and exclude a further 334 (1·9 per cent) patients. They were neither identified as dead by linkage to the registry 'Causes of Death' (see below) nor as living by existing in a register covering the entire Swedish population. These 334 individuals were accordingly included in the inpatient register with an erroneous registration number.

As a result, this study was based on a total of 16 439 patients with an age distribution as shown in *Table 1*. Their mean age at cholecystectomy (±s.d.) was 47·4 (±16·0) years.

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Table 1 *Number of subjects in the cohort and person-years of observation by sex and age at cholecystectomy*

Age at cholecystectomy (years)	Men		Women		Men and women	
	Number	Person-years	Number	Person-years	Number	Person-years
<30	320	5099	2544	41·301	2864	46 400
30–39	731	11 622	1852	29 836	2583	41 458
40–49	1204	18 768	1968	31 529	3172	50 297
50–59	1193	17 366	2353	36 126	3546	53 492
60–69	997	11 958	1937	26 344	2934	38 302
70+	533	4512	807	8024	1340	12 536
All ages	4978	69 325	11 461	173 160	16 439	242 485

Incidence of cancer among the cohort

Since 1958, information concerning all incident cases of malignant disease diagnosed in Sweden has been stored at the National Cancer Registry of the Swedish Board of Health and Welfare. This registry includes the type and location of the tumour according to the ICD code, the place and date of diagnosis, and the diagnostic grounds. The registry was complete for the years up to 1981 at the time of this study. The completeness of the cancer registry is in the order of 95 per cent of all diagnosed malignant neoplasms[20,21]. In one per cent of the cases the NRN entered have been found to be incorrect[22].

In order to identify subjects with a large bowel cancer that was diagnosed subsequent to cholecystectomy, we linked the cohort data with the data in the cancer registry for the period 1964–1981 and obtained information on the occurrence of the cancer in the cohort irrespective of the region in Sweden in which it had been diagnosed.

The closing date of the follow-up was 31 December 1981, which corresponds to 14–17 completed years of observation. At the end of this period, 12 770 patients were still alive, 3577 were dead and 92 were lost to follow-up because of emigration.

Expected cancer incidence

The net size of the cohort for each year after surgery was calculated from the data on death and emigration which we obtained from the computerized national registers 'Causes of Death' and 'Population Changes' at the National Central Bureau of Statistics. This information permitted exact calculation of person-years at risk, starting at the date of cholecystectomy and ending at the date of death, emigration, diagnosis of colonic cancer or at the closing date of this follow-up. The number of person-years is shown by age at surgery, in *Table 1*. In the calculations, however, the data were further classified with respect to sex and 5 year age group for each year of observation.

On the basis of these figures of person-years at risk, the expected number of colonic and rectal cancers were computed by age, sex and each year of observation after cholecystectomy. The calculations were based on the age-specific incidence rates among the entire Swedish population for the period 1964–1970 and for the Uppsala Health Care Region during the remaining period of follow-up. Incidence figures for 1980 were used to calculate the expected number also for 1981.

The present updating disclosed a minor but regrettable error in our earlier communication. The incidence rates for rectal cancer provided by the Cancer Registry included premalignant tumors on that occasion. The number of such tumours notified to the Registry constituted only a small proportion of the invasive rectal cancers and accordingly the resulting error did not have any impact on the overall pattern of results. The expected number of cancer cases was slightly overrated, exaggerating the trend towards a decreased risk of rectal cancer.

Statistical method

The results are presented as relative risks (RR). Under the assumption that the observed number of diagnosed cancers followed a Poisson distribution, the exact 95 per cent confidence limits were computed[23].

Results

The overall risk of colorectal cancer (with 95 per cent confidence limits, CL) was 0·86 (0·64–1·13) for men, 0·93 (0·77–1·16) for women and 0·90 (0·77–1·05) for both sexes combined. A major aim of this updating was to disclose a possible trend towards an increased risk of developing cancer after prolonged follow-up. No such trend was confirmed. Thus, the total number of cancers of the colon diagnosed 12–17 years after cholecystectomy was 27 *versus* 34·4 expected (RR = 0·78; 95 per cent CL 0·52–1·11) and of the rectum 9 *versus* 18·4 expected (RR = 0·49; 95 per cent CL 0·22–0·93). The corresponding risk estimates for the last three years only were 0·43 (95 per cent CL 0·14–1·00) and 0·31 (95 per cent CL 0·04–1·13) for the colon and rectum respectively. Although not significantly differing from unity, these data indicate a decreased rather than an increased risk in the long term.

When the risk of cancer of the colon was related to age at cholecystectomy (*Table 2*), no trend emerged, either among the men or among the women. Although the risk estimates for men were consistently lower than those for women, the confidence limits were wide and the overall risk was close to unity (RR = 0·95; 95 per cent CL 0·76–1·13). The possibility of trends related to duration of observation was analysed as in our earlier study[1]. The relative risk tended to be lower during the last few years of observation than during the whole period (as stated above), but there was no evidence of a regular trend.

The risk of rectal cancer was also seemingly unrelated to age at cholecystectomy (*Table 3*). It should be noted that compared with our previous study[1], the number of new cases of rectal cancer observed during three additional years of follow-up increased by six (14 per cent), whereas the expected number decreased by two (3 per cent). This paradox is predominantly due to the positively biased incidence figures which were applied in the previous analysis, as stated in the Patients and methods section. Nevertheless, the trend towards a decreased risk remained among the women (*Table 3*), with an overall relative

Table 2 *Number of observed and expected cases of cancer of the colon with corresponding relative risk and 95 per cent confidence limits*

Age at cholecystectomy (years)	Men				Women				Men and women			
	O	E	RR	(95 per cent CL)	O	E	RR	(95 per cent CL)	O	E	RR	(95 per cent CL)
<50	3	5·2	0·58	0·12–1·69	11	11·3	0·97	0·49–1·74	14	16·5	0·85	0·46–1·42
50–59	8	9·6	0·83	0·36–1·64	19	19·0	1·00	0·60–1·56	27	28·6	0·95	0·62–1·30
60–69	12	13·6	0·88	0·46–1·54	30	25·8	1·16	0·79–1·65	42	39·4	1·07	0·77–1·43
70+	7	8·8	0·80	0·32–1·64	11	13·6	0·81	0·40–1·45	18	22·4	0·81	0·48–1·28
All ages	30	37·1	0·81	0·55–1·14	71	69·7	1·02	0·82–1·28	101	106·8	0·95	0·76–1·13

O, observed cases; E, expected cases; RR, relative risk; CL, confidence limits

Table 3 *Number of observed and expected cases of cancer of the rectum with corresponding relative risk and 95 per cent confidence limits*

Age at cholecystectomy (years)	Men				Women				Men and women			
	O	E	RR	(95 per cent CL)	O	E	RR	(95 per cent CL)	O	E	RR	(95 per cent CL)
<50	3	3·6	0·83	0·17–2·44	7	5·9	1·19	0·48–2·45	10	9·5	1·05	0·51–1·94
50–59	5	6·8	0·73	0·24–1·72	5	9·7	0·52	0·17–1·20	10	16·5	0·61	0·29–1·12
60–69	13	9·3	1·39	0·74–2·39	11	12·8	0·86	0·43–1·54	24	22·1	1·09	0·70–1·62
70+	3	5·8	0·52	0·11–1·51	2	5·7	0·35	0·04–1·27	5	11·5	0·44	0·14–1·02
All ages	24	25·5	0·94	0·60–1·40	25	34·0	0·73	0·48–1·07	49	59·5	0·82	0·61–1·08

O, observed cases; E, expected cases; RR, relative risk; CL, confidence limits

risk of 0·73 (95 per cent CL 0·48–1·07). A lower risk was seemingly confined to women 50 years of age or older at cholecystectomy (RR = 0·64; 95 per cent CL 0·38–1·01) rather than to those who were younger (RR = 1·19; 95 per cent CL 0·48–2·46). This was an *a posteriori* subgroup analysis which should be interpreted cautiously. There was no regular trend with increasing duration of follow-up.

Discussion

The main contributions to this field during the last few years have been derived from epidemiological studies with use of varying methods[10–19]. Whereas some but not all[18] autopsy studies have provided a certain degree of support for an increase in the risk[16], at least of right-sided[15] colonic cancer in connection with gallbladder disease, a number of case-control studies[10,11,13,14,17,19] have yielded highly contradictory findings. Thus, the concept of a risk increase has been both supported[10,13,19] and refuted[17], and in one study[11] a borderline significance further indicated the need for larger studies in this field. There is also persisting controversy as to whether a gradient for right- *versus* left-sided colonic cancers exists[10,13,19] or not[11,12,17]. Despite the fact that some experimental data link secondary bile acids primarily to rectal cancer, this tumour site has only occasionally been analysed separately[11,19].

Our analysis has shown that patients with surgically confirmed gallbladder disease in Sweden are exposed to a risk of developing large bowel cancer which is equal to or even lower than that of the general population. This will only hold true on condition that patients with gallbladder disease do not have a decreased risk with respect to cancer risk before the operation. To our knowledge there is no evidence for this. The longer observation time, the larger number of cases and the further improved internal validity encouraged us to dismiss the possibility of a significant positive association between cholecystectomy and colorectal cancer in this population, with greater confidence now than at the time of our previous report[1].

The methods employed in this study have been critically reviewed previously[1]. The present analysis was carried out after identification and exclusion of a group of 334 (1·9 per cent) patients in the cohort who contributed with person-years at risk but were not available to follow-up because of a faulty national registration number. In addition, we had access to incidence figures which were more closely adjusted in space and time to the area and period of the study and above all were based on malignant tumours only.

Exclusion of a positive association between cholecystectomy and the risk of large bowel cancer has several important consequences. Firstly, this finding is incompatible with the hypothesis that removal of the gallbladder induces metabolic changes—e.g. related to bile acid excretion or degradation, particularly to an increased proportion of secondary bile acids[2,4]—with a carcinogenic potential. This inference further implies either that such metabolic changes do not occur, or that the carcinogenic effect that has been established in experimental research[2,5,6,8] has no bearing on human conditions. This latter interpretation gained support when van der Linden *et al.*[9] recently found that in patients with gallstone disease a higher proportion of secondary bile acids in the duodenum is a characteristic of the disease already before operation and that it is largely unaltered by removal even of a functioning gallbladder.

Secondly, the concept of tumour promotion in the large bowel in relation to gallbladder disease or cholecystectomy gained no support in our study. A promoting effect might be most easy to confirm among older patients, for different reasons. Promotion requires an antecedent initiation of the neoplastic process and since the prevalence of both premalignant adenomatous polyps and preclinical malignant tumours increases with increasing age, it should increase the likelihood of manifestation of a promoting effect. Moreover, if the promoting effect were non-causally associated with a cholecystectomy, i.e. if it were due to an underlying metabolic characteristic rather than to the surgical procedure[9,19], older patients should (on average) have had a longer duration of exposure. However, we found no trend in the relative risk in relation to age at cholecystectomy.

Thirdly, our findings may have a bearing on the generally held view that cancer of the large bowel and gallbladder disease may have major aetiological factors in common[9,19,24]. Characteristics of sex hormone metabolism and a low fertility have been linked to both these conditions[2,24], but in this cohort we were unable to establish an association with breast cancer[25], which has similar epidemiological risk factors. The area of major interest in this context, however, is dietary habits. It seems well established from experimental research[2,26] that colorectal cancer is causally related both with a low intake of dietary fibre and with quantitative and qualitative aspects of fat intake and this seems reasonable for human conditions[2,27,28].

Obviously our data lend no support to the hypothesis that the same dietary characteristics are linked to the occurrence of gallstones and colorectal cancer—i.e. that these diseases are non-causally related to each other by sharing the same aetiological factors. On the other hand, such an association cannot be definitely ruled out. Establishment of the association requires a certain degree of heterogeneity in the level of exposure within the population. Conclusive data may therefore be difficult to obtain if the entire population have approximately the same dietary habits—or if they are all exposed at a level above the limits within which the risk of large bowel cancer is modified by dietary factors. There is no evidence to support the possibility that such an extreme degree of homogeneity or degree of exposure actually exists in this Swedish population, which was recruited from a large urban and rural area.

We conclude that the finding of an increased risk of colorectal cancer after cholecystectomy, which refers to only one earlier cohort study[29] and which has received additional although highly inconclusive support from a considerable number of case-control studies[10–19], could not be reproduced within 17 years of observation in the present large and population-based cohort analysis. Some minor trends indicating a decreased cancer risk emerged, but the decision as to whether they are due to chance alone or are of biological significance has to await prolonged follow-up of the cohort.

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Natural history of anterior mucosal prolapse

Case notes of 250 patients (M:F, 1:2·7; age 48·7 ± 16·5 years) in whom anterior mucosal prolapse had been diagnosed, at one hospital between 1974 and 1976, were reviewed. The commonest symptoms were bleeding (56 per cent), pain (32 per cent) and a sense of prolapse (32 per cent). The prevalence of constipation was significantly higher among women (47 per cent) than men (29 per cent). Perineal descent was present in 20 per cent of cases and was significantly more frequently associated with excessive straining at defaecation (28 per cent) compared with patients in whom there was no history of excessive straining (12 per cent). Sixty-six patients (26 per cent) experienced recurring symptoms over the 10 year period following presentation but did not deteriorate, while 28 patients (11 per cent) deteriorated. Deterioration was associated with a history of symptoms for longer than 1 year at the time of presentation, female sex, and the presence of perineal descent on clinical examination. The risk of developing perineal descent was < 10 per cent over the 5 years after presentation while that of developing sphincter laxity among patients who had already developed perineal descent was 30 per cent over this period. Complete rectal prolapse occurred in 20 per cent (3/15) of patients with clinical perineal descent and sphincter laxity but was not seen in the absence of these signs. The results of treatment by submucosal phenol injection, mucosal rubber banding, or glycerine suppositories were the same.

Keywords: Defaecation, mucosal prolapse

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The syndrome of the descending perineum was first described in 1966 by Parks, Porter and Hardcastle[1]. They proposed that excessive straining during defaecation could eventually produce symptoms when the anterior rectal wall was pushed into the upper anal canal. They suggested that, at the onset of defaecation, the mobile anterior rectal wall could obstruct the passage of faeces into the anal canal and, at the end of defaecation, it tended to follow the faecal bolus through the anal canal. Although this anterior rectal wall intussusception is probably full thickness, the symptoms are thought to arise mainly from the overlying mucosa and hence it has been called 'anterior mucosal prolapse'. Parks *et al.*[1] also suggested that an important factor in the development of symptoms was loss of the normal tone of the pelvic floor (perineal descent) which resulted in an increase in the anorectal angle leading to a tendency for prolapse of the bulging anterior rectal wall into the anal canal.

While anterior mucosal prolapse can be identified as a physical sign on proctoscopy its significance as an indicator of an underlying defaecation or pelvic floor disorder is uncertain. Similarities between anterior mucosal prolapse and solitary ulcer of the rectum syndrome, in both pathophysiology and histopathology, have been described[2,3]. Both appear to be a consequence of prolapse of the anterior rectal wall into the anal canal[2], and histologically both are associated with fibromuscular hyperplasia in the lamina propria, glandular hyperplasia and thickening of the muscularis mucosae[3]. It has been suggested that these conditions represent a spectrum of one condition for which the name 'mucosal prolapse syndrome' has been proposed[3]. These histopathological features are also found[3] in complete rectal prolapse. The extent to which anterior mucosal prolapse is a precursor of complete prolapse is not clear but the latter is known to complicate 27–49 per cent of cases of solitary ulcer[4–6]. Thus, anterior mucosal prolapse appears to be a physical sign associated with a spectrum of conditions whose pathogenesis includes prolapse of the anterior rectal wall during defaecation. The connection between the natural histories of anterior mucosal prolapse, solitary ulcer and complete prolapse has not been established.

In this study we have attempted to identify the associated symptoms and signs in a group of patients in whom anterior mucosal prolapse was identified. All those attending the out-patient department between 1974 and 1976 were studied, and their course over the next 10 years was followed.

Patients and methods

The case notes of all patients, in whom the diagnosis of anterior mucosal prolapse had been made while attending the out-patient department of one hospital between 1974 and 1976, were studied. Presenting symptoms were those which the patient complained of at the first clinic attendance. Constipation included both reduced frequency of defaecation and increased stool consistency. The diagnosis was established at proctoscopy on observing a prominent fold of redundant mucosa on the anterior rectal wall which protruded into the proctoscope field with abdominal straining (*Figure 1*). This rectal mucosa tended to follow as the proctoscope was withdrawn through the anal canal, occasionally reaching the anal verge. Abnormal perineal descent was noted when there was effacement of the anal sphincter and protrusion of the perineal body associated with a descent of the anus and levator plate to below the level of the ischial spines.

The 2 × 2 contingency table method[7] was used in the analysis of data. Calculation of cumulative probability of perineal descent and sphincter laxity excludes patients lost to follow-up. In the discussion, the assumption is made that patients in the population lost to follow-up had the same, or a more benign , natural history as in the population who were not lost to follow-up.

Results

Presentation

Anterior mucosal prolapse was diagnosed in 250 patients (M:F, 1:2·7; mean age 48·7 ± 16·5 years) attending

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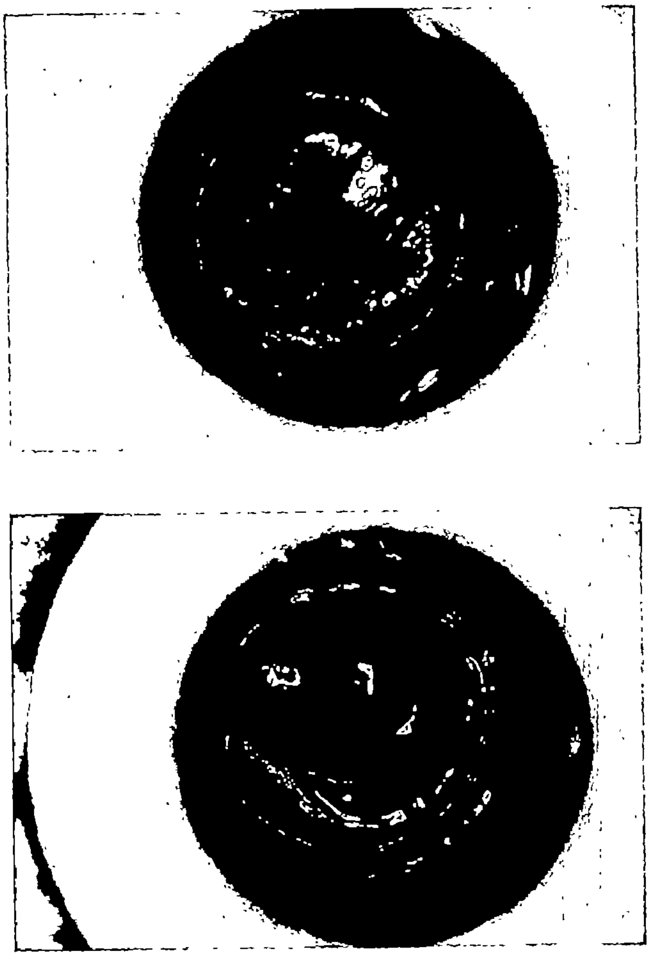

Figure 1 *Proctoscopic view of the anal canal in anterior mucosal prolapse (upper). When the patient strains (lower) the anterior rectal wall (at the top of the field) becomes more prominent and protrudes into the proctoscope, tending to follow as the proctoscope is removed through the anal canal*

between 1974 and 1976. The median duration of symptoms at time of presentation lay between 1 and 2 years (overall range 1 month to > 10 years). The prevalence of presenting symptoms and signs is shown in *Tables 1* and *2*.

The prevalence of constipation (106/250, 42 per cent) was significantly ($P<0{\cdot}02$) more common (*Table 3*) in women (47 per cent) than in men (31 per cent). The prevalence of straining at defaecation (36/250, 14 per cent) was not significantly different among men and women. However, there was a significant ($P<0{\cdot}01$) difference in the prevalence of straining among patients with perineal descent (28 per cent) compared to that of patients in whom perineal descent was not observed (12 per cent).

Treatment

All patients were instructed to avoid excessive straining at stool and given advice about an adequate intake of dietary fibre. Forty-seven (19 per cent) patients did not return after the first clinic attendance. Two hundred and one of the remaining 203 patients were also treated by either phenol injection into the prolapsing rectal mucosa (160 patients), mucosal rubber banding supplemented by phenol injection (25 patients), or glycerine suppositories to encourage complete defaecation (16 patients), and returned for evaluation within 6 months of treatment. Sixty-nine per cent of patients in each of these treatment groups (110, 17, 11 patients respectively) were symptomatically improved within 6 months of initial presentation.

Follow-up

One hundred and nine patients (44 per cent of all patients treated) were noted to be symptomatically improved on their return to the clinic within 6 months of treatment and did not return again to the out-patient clinic during the following 10 years. Sixty-six (26 per cent) patients were initially improved but returned periodically to the out-patient clinic with recurring symptoms during the 10 years follow-up. There was no deterioration of either symptoms or signs in these patients. Twenty-eight (11 per cent) patients progressively deteriorated. The physical signs in these patients at presentation, and those which they developed over the 10 year follow-up period are shown in *Table 4*. The cumulative probability of a patient, seen at least twice at the out-patient clinic, developing perineal descent during the period of follow-up is shown in *Figure 2*; that of a patient with associated perineal descent developing sphincter laxity is shown in *Figure 3*.

Factors associated with deterioration

The proportion of women in the group of patients whose symptoms or signs progressed (M:F, 1:13) was significantly ($P<0{\cdot}01$) greater than the proportion of women in the group who did not progress (M:F, 1:2·4). The prevalence of hysterectomy in the group who progressed (9/26, 35 per cent) was greater than that in the group who did not progress (32/156, 21 per cent), but this difference did not reach statistical significance.

Duration of history of more than 1 year at the time of presentation was significantly ($P<0{\cdot}01$) more prevalent in the group whose signs and symptoms progressed (23/28, 82 per cent) compared with that in the group whose condition did not progress (115/204, 56 per cent). There was no significant difference between the two groups in the prevalence of any of the symptoms shown in *Table 1*. There was no significant difference in the prevalence of a history of either constipation or excessive straining at defaecation in patients whose condition progressed compared with those who did not progress (*Table 3*).

Associated perineal descent was significantly ($P<0{\cdot}01$) more common among patients whose condition progressed (12/28, 43 per cent) than in patients who did not progress (38/222, 17 per cent). Conversely, the presence of anterior mucosal prolapse alone was significantly ($P<0{\cdot}001$) less common in patients whose condition progressed (10/28, 36 per cent) than in patients whose condition did not progress (131/222, 59 per cent).

Table 1 *Presenting symptoms of 250 patients with anterior mucosal prolapse seen between 1974 and 1976*

	Number	Percentage
Bleeding	140	56
Sense of prolapse	80	32
Pain or discomfort	80	32
Pruritus ani	52	21
Mucous discharge	50	20
Sense of incomplete evacuation	40	16
Incontinence	5	2

Table 2 *Presenting physical signs in 250 patients with anterior mucosal prolapse seen between 1974 and 1976*

	Number	Percentage
Anterior mucosal prolapse only	140	56
Haemorrhoids	50	20
Perineal descent	35	14
Sphincter laxity	20	8
Cystorectocoele	20	8
Perineal descent and sphincter laxity	15	6

Table 3 *Prevalence of constipation and straining by sex, presence of clinical perineal descent, and natural history*

	Number of patients	Constipation Number of patients	Constipation P	Straining Number of patients	Straining P
Men	68	21 (31)	<0·02	6 (9)	n.s.
Women	182	85 (47)		26 (14)	
Perineal descent	40	17 (43)	n.s.	11 (28)	<0·01
No perineal descent	210	74 (35)		25 (12)	
Progression of symptoms/signs	28	15 (54)	n.s.	7 (25)	n.s.
No progression	222	91 (41)		29 (13)	

Numbers in parentheses are percentages

Table 4 *Incidence of more severe physical signs developing during the 10-year period after presentation in 28 patients*

Physical signs at presentation	n	New physical sign developing within 10 years	n	Proportion of patients at risk who developed new physical sign (%)
Anterior mucosal prolapse alone	200	Solitary ulcer	9	5
		Perineal descent	10	5
		Sphincter laxity	2	1
Anterior mucosal prolapse with perineal descent	35	Sphincter laxity	7	20
Anterior mucosal prolapse with perineal descent and sphincter laxity	15	Complete rectal prolapse	3	20

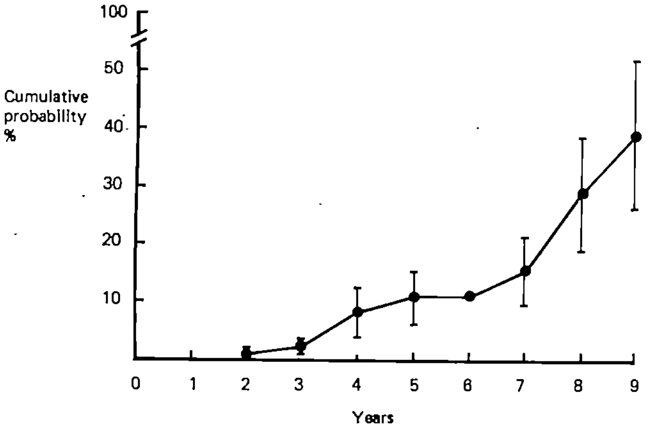

Figure 2 *Cumulative probability that a patient with anterior mucosal prolapse, attending the out-patient clinic, will develop clinically diagnosed perineal descent over the next 10 years*

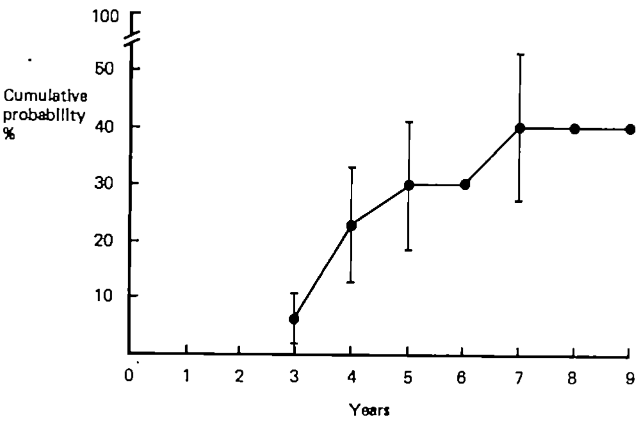

Figure 3 *Cumulative probability that a patient with anterior mucosal prolapse associated with clinically diagnosed perineal descent, attending the out-patient clinic, will develop sphincter laxity over the next 10 years*

Discussion

This retrospective review can provide only a limited impression of the presentation and outcome of anterior mucosal prolapse. Follow-up has relied on the patient returning to the out-patient clinic when further symptoms arise, and we do not know whether the 63 per cent of patients who did not return beyond 6 months from presentation experienced further symptoms. However, this is the only available information concerned with this condition and should stimulate prospective studies.

The most frequently encountered symptoms of bleeding, pain and a sense of prolapse are virtually identical to those of haemorrhoids[8]. It is possible, on proctoscopy, to differentiate anterior mucosal prolapse from haemorrhoids and conditions where rectal mucosa may be seen in the anal canal e.g. after fistula surgery or a Whitehead haemorrhoidectomy. Some protrusion of the anterior rectal wall can be seen normally, particularly if the proctoscope is angled anteriorly, and the reproducibility of this physical sign, between different observers, is not known. There is a need for a reliable method of measuring the extent of anterior mucosal prolapse. In this study 24 per cent of patients, in whom anterior mucosal prolapse was the only abnormal physical sign, experienced recurring symptoms during the 10-year period after initial presentation, and 5 per cent progressed to develop worsening symptoms and perineal descent. In these patients anterior mucosal prolapse appears to have been the prodromal physical sign of a defaecation disorder. It tended to occur more frequently in women than in men, and affected women were six times more likely to deteriorate than affected men. The prevalence of hysterectomy (35 per cent) among women who deteriorated was more than double that (<15 per cent) which would be expected in the normal age matched population[9]. A number of factors may explain this preponderance in women.

It has been suggested that excessive straining at defaecation is a cause of anterior mucosal prolapse[1]. This is consistent with the increased prevalence of constipation which we found in women compared with men (*Table 3*). The prevalence of excessive straining was lower in our study (14 per cent) than that previously reported[1] in a selected group of patients with an abnormal degree of perineal descent (83 per cent). Although a history of straining should rely on objective criteria e.g. time spent in the toilet, an accurate assessment of the force and time spent straining requires measurement. Questioning of the patient may also introduce bias, in that the patient tends to concur with the doctor's explanation of symptoms. Only 50 per cent of our patients gave a history of constipation or straining; thus, our study does not support the view that anterior mucosal prolapse is invariably associated with excessive straining.

Increased mobility of the anterior rectal wall may also be a factor. In the female the only restraining attachment to the anterior rectal wall is the vagina which is attached to the pelvis by the ligaments of the cervix and uterus[10]. When standing, if intra-abdominal pressure is inadvertently raised by coughing or lifting, the uterus, cervix and anterior rectal wall are forced down onto the posterior wall of the rectum which is supported horizontally on the levator ani[11]. Laxity of the uterosacral and transverse cervical ligaments with ageing or as a result of childbirth[12], or their division after hysterectomy, might increase mobility of the anterior rectal wall.

Finally, anterior mucosal prolapse may produce symptoms when the anorectal angle is increased through loss of tone in the pelvic floor[1]. The finding that 80 per cent of affected patients did not have perineal descent suggests either that symptoms occurred in the absence of a lax pelvic floor or that the clinical diagnosis of pelvic laxity was insensitive. The association of perineal descent with an increased risk of progression of symptoms and signs during the following 10 years (*Table 4*) suggests that there is some validity in the clinical assessment of perineal descent made in these patients.

Five per cent of patients were observed to develop ulceration on the prolapsing rectal mucosa. This supports the suggestion[2] that prolapse of the anterior rectal wall can be a cause of rectal ulceration. The mean age of onset of complete rectal prolapse occurs two decades later[13] than the mean age of our patients. Our follow-up may not be sufficient to establish the incidence of complete prolapse in this population of patients. Perineal descent and sphincter laxity were present in the three cases of complete prolapse which developed in our patients. Most cases of complete prolapse are not associated with pelvic floor weakness, assessed either clinically[14] or radiologically[15]. Thus, complete prolapse in patients with a normal pelvic floor may have a different pathogenesis to that found in association with anterior mucosal prolapse. In the former, complete prolapse probably originates as a rectal intussusception at a higher level than anterior mucosal prolapse[16,17]. Patients with a paralysed pelvic floor are vulnerable to complete prolapse[18], and it is possible that the association between anterior mucosal prolapse and complete prolapse is dependent on the degree of pelvic floor weakness rather than the presence of anterior mucosal prolapse.

Treatment with local injection of phenol or rubber band ligation was not superior to medical measures alone.Symptomatic improvement in 69 per cent of patients at 6 months may be a reflection of the tendency for symptoms to remit spontaneously. Initially, when symptoms develop in the absence of clinically detectable perineal descent, the risk of deterioration is small (*Figure 3*) and symptoms may be controlled by advice to avoid constipation and excessive straining at defaecation. Hysterectomy, by reducing support of the anterior rectal wall, may aggravate the symptoms. In advanced cases, where the pelvic floor is grossly lax, the least amount of straining during normal daily activity will aggravate symptoms and these patients are not greatly relieved by straining less during defaecation. Many patients accommodate to their symptoms but once this advanced stage is reached the risk that sphincter laxity, arising from a pudendal nerve traction neuropathy[19], will develop over the next 5 years is about 30 per cent (*Figure 3*).

Development of some degree of anterior mucosal prolapse may be part of the normal ageing process—particularly in women. In the majority of patients the symptoms follow a benign course, but in approximately one in ten patients the problem of treating progressively worsening symptoms in unsolved.

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Implantation of a pressure cuff around the subphrenic oesophagus

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The possibility of implanting a pressure cuff around the subphrenic oesophagus as a barrier to reflux was tested in six pigs. The oesophagus tolerated cuff pressures from 48 to 95 cmH_2O, corresponding to intra-oesophageal pressures from 27 to 75 cmH_2O. The pigs with the perioesophageal cuff swallowed a solid diet without difficulty. However, dysphagia occurred in pigs kept alive for more than a month and the main reason was malfunction of the device because of surrounding fibrosis. This problem should be solved before implantation of the device in humans is attempted.

Keywords: Oesophagus, lower oesophageal sphincter, artificial perioesophageal pressure device, gastro-oesophageal reflux

Artificial sphincters have been successfully implanted around the bladder neck or urethral bulb as a treatment of urinary incontinence[1-3]. Implantation of an artificial pressure device around the subphrenic oesophagus was tested in six pigs.

Methods

The artifical pressure device is constructed of silicone rubber. It consists of an inflatable snap-on cuff connected by a tube to a balloon which maintains the fluid pressure within the system at a preset level (American Medical System, USA) (*Figure 1*). With the pig in general anaesthesia the abdomen was opened through an upper midline incision. The subphrenic oesophagus was bluntly mobilized and encircled by the cuff without including the vagi. The balloon was placed below the left lobe of the liver, connected to the cuff, and the system was filled with 18 ml isotonic radiopaque solution (Hypaque 25 per cent and sterile water in equal parts). A gastrostomy was constructed with a 30 F Pezzer catheter. Ampicillin 1 g and streptomycin 0·5 g were given intra-operatively.

For 4 days the pigs were maintained on intravenous fluids, then allowed free access to fluid nutrients (Fresubin, Kabi Vitrum, Sweden) and after a week given commercial, solid pig fodder. The gastrostomy catheter was closed from the fourth day.

Fluid and solid barium meals were performed one week after implantation of the device and just preceding death.

At a laparotomy preceding death, the intraluminal oesophageal pressure was measured by an open-tip 125 cm long polyethylene catheter (Clay Adams, PE 160, 1·14/1·57 mm diameter) ending in a metal tip with three holes at the same level placed 120° apart. A continuous flow of 30 ml/h was used and the signals were recorded by a strain-gauge transducer (Statham P23ID) on a pen recorder (Elema-Schonander 81)[4]. The mean of two recordings at different rotations of the catheter was used. The desired level of the catheter tip was secured by means of a string tied to the tip end emerging through a gastrotomy.

Microscopic examination was done on sections made from the oesophagus above, at, and below the level of the cuff.

Results

Table 1 summarizes the results. In pig no. 4 the intraluminal pressure at cuff level was measured at varying pressures in the balloon (*Figure 2*), and the pig was killed. The postoperative course in the other five was uneventful, and they were able to eat after 4 days. The barium meal studies showed free passage of fluids and solids. When the bolus passed the cuff, fluid was displaced from the cuff to the balloon as viewed on X-ray. Pigs numbers 3, 5 and 6 stopped eating solids 4–9 weeks postoperatively and X-ray showed that fluid could no longer move freely from the cuff to the balloon. However, liquids could still pass to the stomach in squirts.

At laparotomy preceding death the intraluminal pressure at the level of the cuff in three pigs (1, 5 and 6) was 27–75 cmH_2O. In all pigs the oesophagus was grossly and microscopically normal, and especially without signs of ischaemia or hypertrophy. A layer of fibrotic tissue of varying thickness without signs of infection enveloped the balloon and the cuff, and in pigs numbers 3 and 5 prevented the balloon from expanding. In pig number 6 the connecting tube was kinked, which explained the malfunction of the system.

Discussion

Our experiments showed that the porcine oesophagus is well able to tolerate a cuff pressure from 48 to 95 cmH_2O and that swallowing of food takes place without difficulty. However, in two pigs a fibrous coating developed around the balloon and consequently the cuff could not relax and could no longer pass solids. Although pigs are more disposed to desmoplasia than man[5], this phenomenon has also caused malfunction of a few urinary artificial sphincters in humans where the balloon was also placed in the peritoneal cavity[2,3]. This problem should be solved before implantation in humans is attempted. Perhaps the balloon should be placed subcutaneously, where the desmoplastic reaction is less and the balloon, if strangulated, can be easily changed. The manufacturer is trying to develop a balloon with lesser desmoplastic properties. Tube kinking caused malfunction in one case, but non-kinking tubes have since become available.

In humans, the diameter of the cuff should not be less than 3·2 cm (cuff circumference of 10 cm) allowing the passage of larger pieces of food. The cuff pressure should be between 40 and 50 cmH_2O to ensure a median intra-oesophageal pressure of 21 cmH_2O as observed in normal subjects[4].

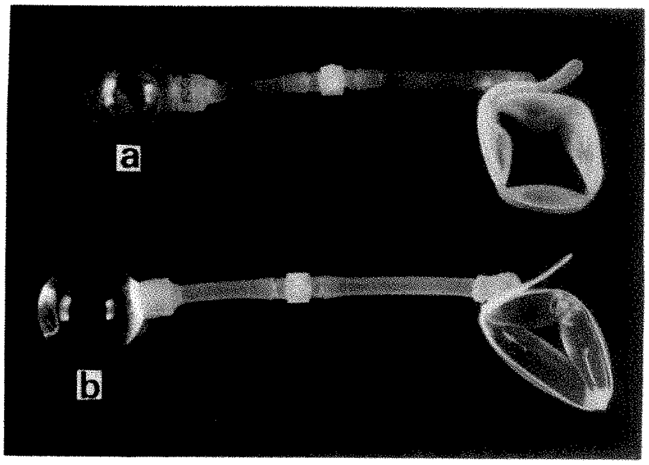

Figure 1 *Perioesophageal pressure device.* **a**: *Before filling with fluid.* **b**: *After filling with 18 ml fluid*

Table 1 *Experimental data and autopsy findings in six pigs with pressure cuff around the subphrenic oesophagus*

Pig no.	Weight of pig (kg)	Cuff diameter (cm)	Balloon pressure (cmH$_2$O)	Intraluminal oesophageal pressure (cmH$_2$O)*	Observation period (weeks)	Autopsy findings
1.	25	1·9	95	75	4	Oesophagus normal, device functioning, surrounded by a thin fibrous capsule
2.	25	1·9	50	No measurement	4	Oesophagus normal, device functioning, surrounded by a thin fibrous capsule
3.	25	1·9	50	No measurement	7	Oesophagus normal, the cuff overfilled and tense and the balloon squeezed by a fibrous capsule
4.	70	3·2	Various pressures applied	—	0	
5.	70	3·2	54	30	4	Oesophagus normal, the cuff overfilled and tense and the balloon squeezed by a fibrous capsule
6.	70	3·2	48	27	9	Oesophagus normal, device functioning but the tube kinked

* See *Figure 2*

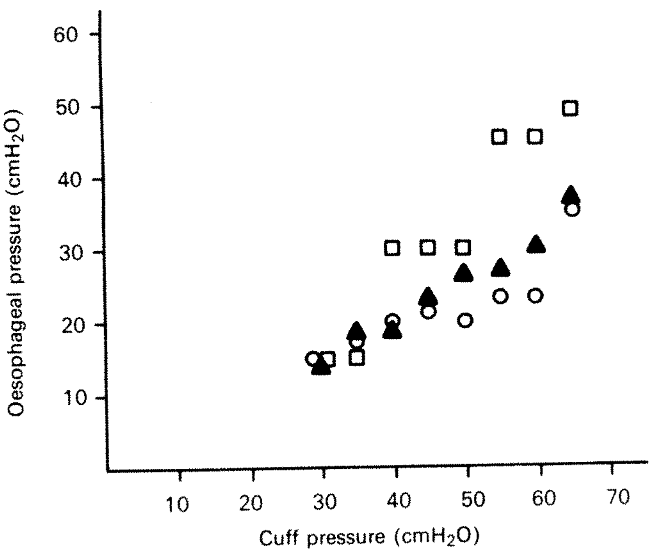

Figure 2 *Variations in the intraluminal oesophageal pressure in relation to the cuff pressure.* ○, *Pig no. 4;* □, *pig no. 5;* ▲, *pig no. 6*

In the pigs a gastrotomy was used to prevent postoperative distension which might have occurred because of difficulty in belching, but a nasogastric tube should suffice in humans.

Theoretically, the pressure device has several advantages over a rigid ring-shaped prosthesis, the Angelchik device used widely in the treatment of gastro-oesophageal reflux[6]. The intraluminal oesophageal pressure may be graded, and if necessary the pressure device can be deactivated percutaneously by ultrasonically guided fine-needle aspiration. The potential advantage over fundoplication, another antireflux operation, is avoidance of extensive surgery that irreversibly changes the anatomy. Furthermore a pressure device that produces constant and known closing pressure would provide more predictable long-term results.

In conclusion, our study showed that it is possible to apply a pressure device around the subphrenic oesophagus and that it works as expected. However, human experimentation, e.g. comparison with fundoplication, requires a balloon with lesser or no desmoplastic properties.

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Partial and complete sternotomy for blunt oesophagectomy

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Oesophagectomy without formal thoracotomy for intrathoracic carcinoma developed during the early twentieth century, was replaced by formal thoracotomy, then reintroduced for palliation of incurable intrathoracic oesophageal cancer[1], and is now selectively applied in the treatment of adenocarcinoma of the lower oesophagus and cardia[2,3]. The technique is often greatly facilitated by partial or complete sternotomy.

Patients

Partial or complete sternotomy was performed in 61 patients: 20 women, 41 men, aged 35 to 88 years (mean 60·7 years). Oesophageal squamous carcinoma was present in 28 of which 2 were cervical and 24 intrathoracic. The tumour was adenocarcinoma or undifferentiated in 33. Three patients had carcinoma of the whole oesophagus discovered at operation, of which two were squamous, one was adenocarcinoma.

Technique

Subcutaneous midline lower sternotomy

This was used in 52 patients to improve access to the upper abdomen[4,5], allowing tumours of the lower oesophagus or cardia of the stomach to be mobilized under direct vision. In those patients in whom there is no advantage in removing the spleen, good access reduces the chance of inadvertent damage when isolating, ligating and dividing the short gastric vessels.

At the upper end of the vertical epigastric incision the two diaphragmatic slips are dissected free from the under surface of the xiphoid process, which may be removed separately or split with the sternum. The skin and subcutaneous tissues are freed from the sternum in the midline by inserting closed Mayo scissors and gently opening them. A forefinger separates the pericardium and pleura from the deep surface of the sternum while the deep blade of a large straight bone-cutting forceps is inserted beneath it. The superficial blade of the forceps is guided into the space between the upper surface of the sternum and the skin and subcutaneous tissue. The forceps are held strictly in the midline as the sternum is cut. Further bites are taken, if necessary up to the manubriosternal joint (*Figure 1*).

A large pack is pushed firmly between the sternal halves, acting as a wedge to separate them, at the same time preventing oozing from the cut bone edges. When the wound is closed, the bone edges are not re-apposed. The upper stitch picks up the linear alba and the two xiphisternal slips of diaphragm on each side.

Excision of the sternoclavicular joint and medial clavicle

A quadrant of the upper manubrium may be excised together with the medial third of the clavicle on one side[6], to increase the effective circumference of the thoracic inlet and allow the stomach or colon to be brought easily into the neck.

The lower end of the cervical incision, running along the anterior border of the sternomastoid muscle, is extended vertically downwards in the midline for 5–7 cm. The skin and subcutaneous tissues are elevated to expose the sternoclavicular joint and medial clavicle. A finger is gently inserted into the suprasternal notch and behind the manubrium into the superior mediastinum, between the sternohyoid and sternothyroid muscles on each side. With a Lebsche knife, stout bone-cutting forceps or a reciprocating saw, the manubrium is divided in the midline to the level of the lower border of the sternoclavicular joint. A lateral cut is made to just above the first rib insertion on the side that will accommodate the conduit. The manubrium, sternoclavicular joint and clavicle are gently elevated from the deep structures so that the clavicle can be safely divided at the junction of its medial and middle thirds (*Figure 2*). If necessary a portion of the anteromedial end of the first rib can be excised[7]. Safe division of the strong, thick manubrium can be tedious, and I have used this technique on only three occasions. There is no need to repair the defect.

Upper midline sternotomy

This allows access for direct dissection of tumours of the upper or middle third of the oesophagus[8]. If the stomach or other conduit appears to be too short to reach to the neck, anastomosis to the oesophagus in the anterior upper chest is possible, provided the cervical oesophagus has not been extensively mobilized and its blood supply compromised.

The cervical incision is extended downwards in the midline

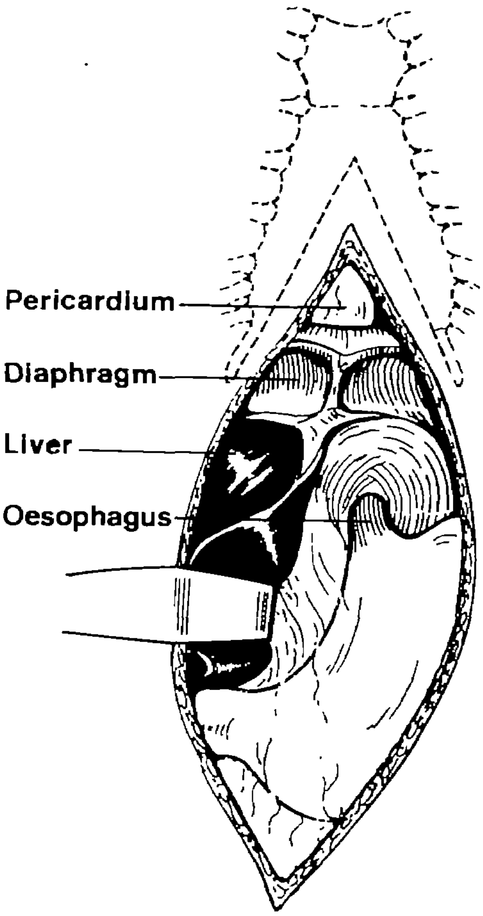

Figure 1 *Subcutaneous midline sternotomy*

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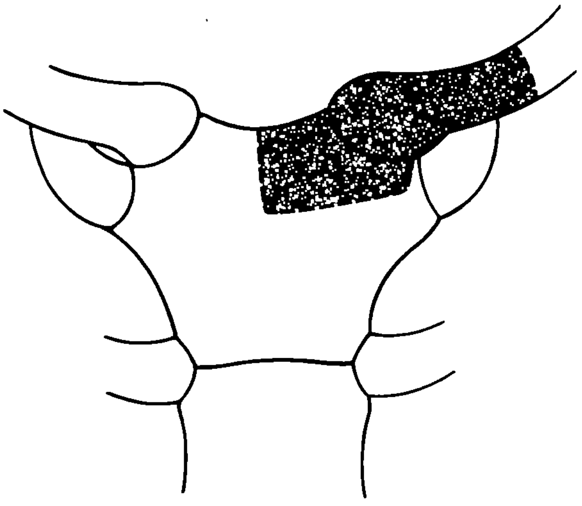

Figure 2 *An upper quadrant of the manubrium, the sternoclavicular joint and the medial third of the clavicle may be removed*

to the middle of the sternum. A finger is gently inserted into the suprasternal notch and behind the upper sternum. With a Lebsche knife or reciprocating saw the sternum is split in the midline as far as the first 1–2 cm of the gladiolus (*Figure 3*). The edges are separated using a self-retaining retractor. The left innominate vein lies immediately beneath the sternum, and if necessary it can be transfixed, ligated and divided to improve access to the oesophagus, seen projecting to the left behind the trachea, which lies between the innominate artery and the left common carotid artery. Care should be taken not to damage the left recurrent laryngeal nerve which passes from beneath the arch of the aorta into the tracheo-oesophageal groove.

The sternum is repaired using strong nylon sutures mounted on trocar pointed needles passed into the marrow cavity of the split sternal edges and thrust through the anterior cortex, to be tied firmly. The skin is closed over the repaired split.

I have used this technique only once, when the stomach reached the neck only under tension and with congestion. Upper midline sternotomy allowed the anastomosis to be made in the upper mediastinum without tension. Because lower midline subcutaneous sternotomy is used almost routinely, I prefer to gain extra access when necessary by its conversion into a complete midline sternotomy.

Complete midline sternotomy

This was originally described[9] separate from the abdominal incision, but it is best combined with the abdominal approach[10]. Excellent access is provided to middle and upper third tumours and can be improved still further by incising the right pleura. It provides access equal to that obtained at right thoracotomy, without the need to turn the patient, and is far superior to anterior thoracotomy[11]. This is in addition to the unsurpassed view of the lower oesophagus and cardia, allowing radical clearance of the coeliac and adjacent lymph glands. For this reason it is important to make the decision to use the technique early in the operation in order to exploit its full benefits throughout.

When blunt oesophagectomy is used for dealing with carcinoma at or near the gastric cardia, the stomach may be shortened by the resection so that it will not reach up to the neck. Provided the cervical oesophagus has not been excessively mobilized to compromise its blood supply, the anastomosis can be easily performed in the anterior mediastinum just above the aortic arch.

I have used this approach on five occasions. In three patients, when dealing with carcinoma near the cardia, it was feared that insufficient stomach would be left to reach the neck. The thoracic oesophagus alone was mobilized and the anastomosis made comfortably in the anterior mediastinum at the upper level of the aortic arch. In two patients with adherent middle third tumours it facilitated mobilization when the index finger inserted in the neck could not reach the point of fixation.

The cervical incision along the anterior border of sternomastoid muscle is extended to the midline at the suprasternal notch. If sternal splitting is preplanned, the cervical incision need not be carried as high as when it is used separately. The vertical upper abdominal midline incision is made and the diaphragmatic slips are dissected from the under surface of the xiphoid process. A finger is inserted in the midline along the under surface of the sternum, from above and below, separating the structures from the bone, care being taken to avoid damaging the pleura. The two skin incisions are joined over the middle of the front of the sternum (*Figure 4*), and the sternum is now split from top to bottom in the midline, using a reciprocating circular saw or a Gigli saw. The pleura is gently separated from the edges as the halves are gradually parted using a ratchet sternal retractor (*Figure 5*).

The main structures are identified. If necessary the innominate vein can be transfixed, ligated and divided. Exceptionally the view of the retrocardiac oesophagus can be improved by making a vertical incision in the right pleura, repairing it subsequently. The gastric or other conduit may be brought up through the posterior mediastinum. Alternatively it can be led in front of the heart, and this is valuable when performing palliative operations since residual posterior mediastinal tumour occasionally invades a conduit led posteriorly. The anastomosis can be accomplished with great ease by drawing the upper thoracic oesophagus forward.

At the completion of the operation the sternum is closed using 8–12 stout nylon sutures mounted on robust trocar-pointed curved needles which penetrate the outer cortex and the marrow cavity. The sutures must be firmly tied to preclude movement between the two halves of the sternum and the skin is then closed over the suture line. If the pleura has been breached, appropriate extra underwater sealed chest drains should be inserted.

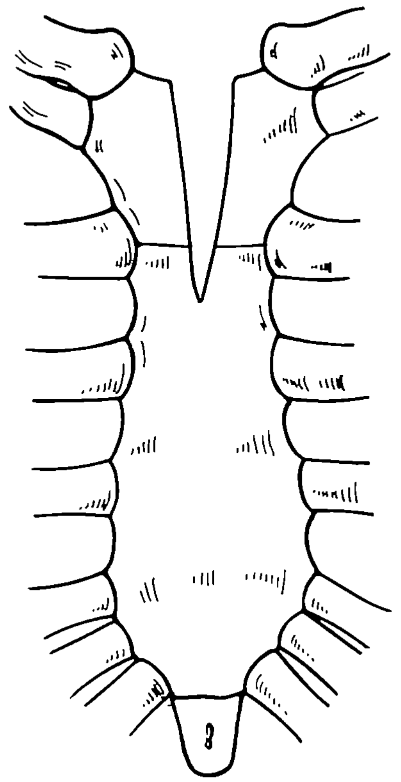

Figure 3 *The manubrium and upper gladiolus may be split*

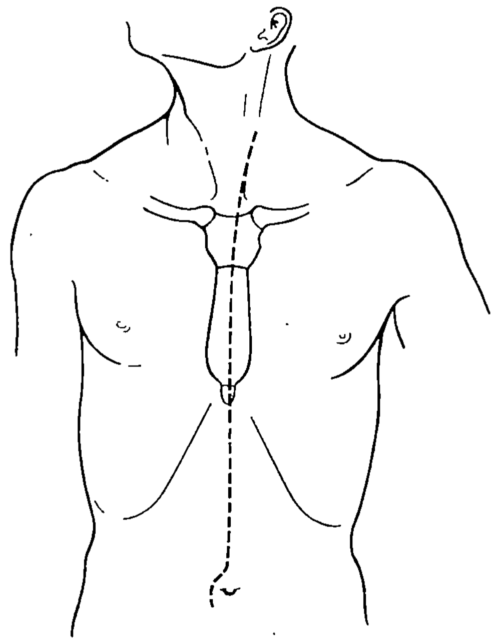

Figure 4 *The cervicosterno-abdominal incision is indicated by the dotted line*

Discussion

Of the 61 patients treated by sternotomy, 17 (28 per cent) died in hospital. Resection was abandoned in 11 patients, 5 of whom died (1 with broncho-oesophageal fistula, 2 from cardiorespiratory failure and 2 from septicaemia). Of the remaining 12 deaths, 6 were cardiorespiratory, 2 patients developed leaks, 1 developed septicaemia without demonstrable leak, 1 died following relief of simple intestinal obstruction, 1 died from rapid recrudescence of the tumour and in 1 the cause of death was not established. The high mortality was related to the age and infirmity of many of the patients and the advanced disease found in almost all of them. None of the deaths could be attributed to the sternotomy.

There were no complications of sternotomy. However, a single complication was indirectly associated with total midline sternotomy in that a late leak developed following substernal oesophagogastrostomy. The track discharged at the upper end of the abdominal wound but the sternal halves became loose. The sternum was re-opened, a distal feeding duodenostomy was inserted through the gastric antrum, the small leak was drained and the sternum was firmly closed. The leak sealed and the patient made a full recovery.

It is important to make a decision to perform one or other form of sternotomy as early as possible in the procedure, otherwise much of the benefit of improved exposure is lost. Once the facility with which the operation can be accomplished is appreciated, generous subcutaneous midline sternotomy becomes almost routine. Using these techniques, all operations for carcinoma of the oesophagus can start with the patient supine and with the skin prepared from the chin to below the umbilicus. It will not be necessary to turn the patient during the operation.

One of the greatest dilemmas encountered by the oesophageal surgeon is the discovery that the conduit will not reach the upper cut end of oesophagus. If there is a gap, then it must be shortened or the conduit lengthened. If neither can be achieved, a new conduit must be formed or the two ends must be brought temporarily to the surface. The gap may be shortened by joining the conduit not to the cervical oesophagus but lower down in the thorax.

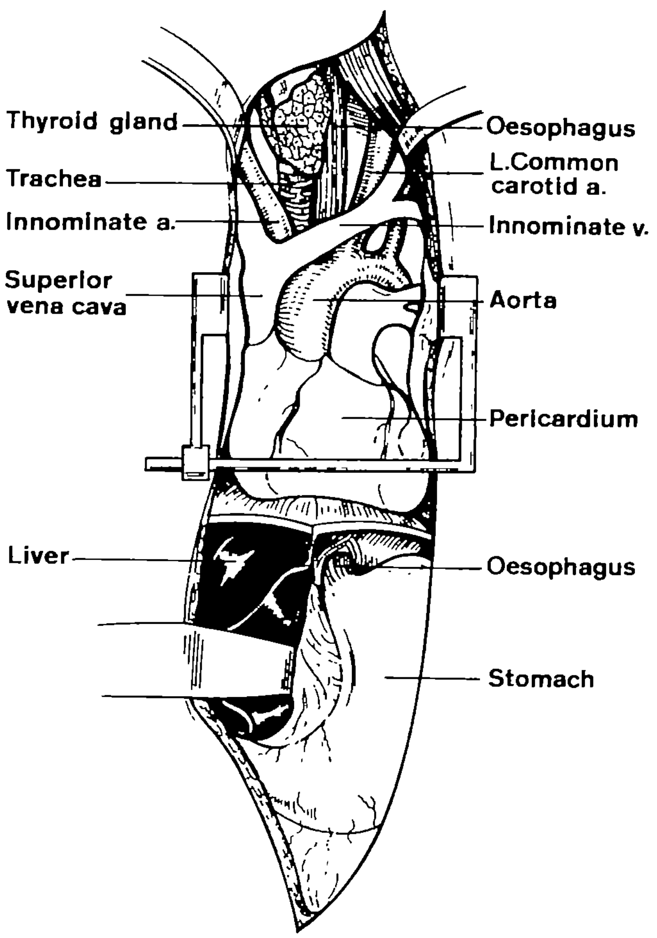

Figure 5 *The exposure produced by the combined incision*

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Edrophonium provocation test in the diagnosis of diffuse oesophageal spasm

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Criteria for diffuse oesophageal spasm(DOS) are dysphagia and chest pain with oesophageal manometry showing retention of peristalsis with the presence of synchronous contractions in response to wet swallows. Because of the intermittent nature of the symptoms, edrophonium was used as a provocative agent to increase diagnostic yield. Three hundred and ninety-six patients underwent transnasal manometry using a Gaeltec system of six internal transducers arranged at 5 cm intervals from the catheter tip; the majority of these patients received 10 mg edrophonium as an intravenous bolus. Reproduction of symptoms with typical manometry of DOS indicated a positive provocation test. There were no significant side effects. DOS was diagnosed in 34 patients who had either the typical manometry or a positive provocation test. Thirty of these patients received edrophonium. Twenty patients had baseline manometry which was diagnostic and ten of this group had a positive provocation test. The remaining 10 patients, who had normal baseline manometry, had positive provocation tests following the injection of edrophonium. Without edrophonium provocation testing, about a third of patients would not have been diagnosed as having DOS.

Keywords: Oesophageal disorders, diffuse oesophageal spasm

Diffuse oesophageal spasm (DOS) is characterized by symptoms of intermittent chest pain or dysphagia or both and is confirmed by the finding of abnormal non-peristaltic contractions with preservation of peristalsis on manometric examination[1]. Because of the intermittent nature of the symptoms, various pharmacological agents have been used to provoke the patients' symptoms and increase the diagnostic yield. Edrophonium (Tensilon) is a very short acting anticholinesterase and seems to be the most effective agent to reproduce the symptoms and manometric abnormalities of DOS with minimal side effects[2,3]. This study assesses the usefulness of the edrophonium provocation test in the diagnosis of diffuse oesophageal spasm.

Methods

All patients referred to the oesophageal laboratory underwent oesophageal manometry using a Gaeltec system which has six intra-oesophageal microtransducers arranged at 5 cm intervals from the tip of the catheter. The manometry was performed in the sitting position with transnasal intubation after a 4 h fast. The lower oesophageal sphincter pressure was measured using the station pull-through technique and then oesophageal contractions were recorded in response to 5 ml boluses of water (wet swallows). DOS was diagnosed in patients who had dysphagia or chest pain and whose manometry showed both (a) more than 30 per cent simultaneous contractions in response to wet swallows and (b) retention of peristalsis with normal lower oesophageal sphincter function to differentiate DOS from achalasia, with additional optional features of (c) amplitude of contraction of more than 200 mmHg, (d) duration of contraction of longer than 7 s and (e) repetitive activity (*Figure 1*).

The majority of patients were then given edrophonium chloride (Tensilon, Roche) 10 mg as an intravenous bolus. This dose has been shown to produce a maximal response in oesophageal contractions[2]. Immediately after the injection, further wet swallows were recorded and the patient's symptom response was recorded, noting in particular chest pain and dysphagia and how these symptoms compared with the patient's usual symptoms. A positive test reproduced the patient's symptoms with the production of a manometric abnormality of DOS.

Results

Since 1983, 396 patients have undergone manometry and 356 patients (90 per cent) have also received an edrophonium provocation test. Thirty-four patients (9 per cent) were diagnosed on either manometric criteria or positive provocation test as having DOS. There was an equal sex distribution with a median age of 50 years (range 14–79). Chest pain was the

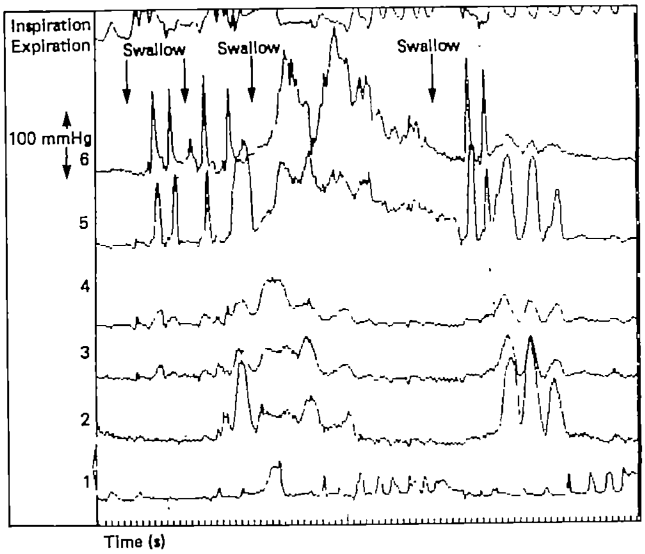

Figure 1 *Manometry tracing of DOS showing repetitive synchronous contractions in response to wet swallows with normal lower oesophageal sphincter function. Recording 1 is at the level of the lower oesophageal sphincter with the other recordings 5, 10, 15, 20 and 25 cm above the sphincter. Normal peristalsis was seen elsewhere in the recording but is not shown in this example*

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Table 1 *Results of the edrophonium provocation test*

	Edrophonium positive	Edrophonium negative	No edrophonium	Total number
Manometry positive	10	10	4	24
Manometry negative	10	0	0	10

presenting symptom in 80 per cent of patients and dysphagia in 60 per cent. Both symptoms were present in 14 patients (40 per cent).

The results of the edrophonium provocation test on these 34 patients are shown in *Table 1*. The remaining patients did not have the manometric criteria of DOS and all had negative edrophonium provocation tests. Before the edrophonium injection, 24 of the 34 patients had baseline manometry which was diagnostic of DOS. Ten of those patients with positive manometry experienced their usual symptoms of chest pain or dysphagia with worsening of their manometric abnormality following the injection of edrophonium and ten had a negative provocation test as their symptoms were not reproduced by the edrophonium. Four patients did not receive edrophonium. The remaining 10 patients (29 per cent of the total) had normal, i.e. negative, manometry initially. Following edrophonium they developed their usual symptoms and produced a manometric pattern compatible with DOS. There were no significant side effects from edrophonium injection although several patients experienced transient abdominal colic or blurred vision.

Discussion

DOS was diagnosed in about 10 per cent of the patients referred to our oesophageal laboratory. This percentage is similar to that reported by Castell[4] and probably relates to the similar criteria used for diagnosis. Using the Gaeltec system, our upper limit of normal amplitude is 200 mmHg which is higher than is usually obtained using a water-perfused system. Other workers might consider amplitudes of this magnitude to be in the 'nutcracker oesophagus' range. All our patients with DOS had synchronous contractions associated in some cases with high amplitude contractions and do not therefore fulfil the criteria for the 'nutcracker oesophagus'[5]. Ten of the patients who had positive baseline manometry had a false negative provocation test. We accept that this may occur and may be related to the intermittent nature of symptoms. Our definition of a positive provocation test required both the reproduction of symptoms and typical abnormal manometry.

The ten patients, who initially had normal manometry and then had a positive provocation test, might be considered to represent false positive results. We do not consider that this is the case. Several patients had the typical radiology of diffuse spasm in addition to a positive provocation test. The injection of edrophonium rapidly reproduced their typical symptoms with associated manometric abnormality although prior to injection they had been asymptomatic with normal manometry. In our experience, the edrophonium provocation test does not produce symptoms nor manometric abnormality of DOS in patients with gastro-oesophageal reflux. A third of our patients with positive manometry have had good symptomatic relief from balloon dilatation and 75 per cent of those with a positive provocation test are now symptom free. If their symptoms were related to reflux, balloon dilatation would probably worsen the situation.

Gastro-oesophageal reflux was not a predominant feature as judged by the Bernstein acid perfusion test and ambulatory 24 h pH recording and we consider that these patients had primary DOS.

In the United States approximately half a million patients a year have a coronary arteriogram for chest pain. At least 10 per cent of these will be normal and Richter has suggested that up to 75 000 patients may have an oesophageal motility disorder causing their pain[1]. There is probably a similar proportion of patients in the United Kingdom with chest pain of oesophageal origin.

It is often difficult to prove a causal relationship between a manometric abnormality and the patient's symptoms unless these occur during the recording. Edrophonium provocation testing seems to increase the likelihood of this happening. In this study almost 30 per cent of patients would not have been diagnosed as DOS without edrophonium provocation testing as their baseline manometry was normal. We have found the edrophonium provocation test to be well tolerated by a large number of patients and we recommend its routine use in conjunction with manometry in the investigation of oesophageal disorders.

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Intracystic injection of OK-432: a new sclerosing therapy for cystic hygroma in children

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Nine patients with cystic hygroma were treated with a new sclerosing therapy consisting of intracystic injection of OK-432 (group A Streptococcus pyogenes *of human origin). Favourable results including complete regression in eight patients and marked regression in one were observed within 2–3 months without serious side-effects except for fever of 2–3 days' duration and local inflammatory reaction lasting for 3–4 days. Local inflammatory reaction did not cause any damage to the overlying skin and did not lead to scar formation.*

Keywords: Cystic hygroma, cystic lymphangioma, sclerosing therapy, OK-432

Surgical excision is thought to be the treatment of choice for cystic hygromas in children[1–3]. However, 75 per cent of these lesions are observed in the neck and extend deeply into vital structures[4]. Therefore, facial nerve palsy and recurrent nerve palsy have occurred in some cases[5–7]. On the other hand, when a portion of the cystic tumour is left, the recurrence rate is reported to be 10–15 per cent[1].

Non-surgical treatment of these lesions has been attempted, but the results have not been satisfactory[5–8]. We have developed a sclerosing therapy with OK-432 (Picibanil[9–13]; Chugai Pharmaceutical Co., Tokyo) for these lesions. This report describes our results in the treatment of cystic hygromas in children.

Patients and methods

Nine patients were treated by intracystic injection of 0·1 mg OK-432 in 10 ml physiological saline solution, immediately after the aspiration of as much intracystic fluid as possible. The dose of OK-432 in each case depended on the amount of aspirated fluid or size of the tumour. When cystic hygromas were mainly composed of a few large cysts and intracystic fluid was easily aspirated, the same amount or less of the OK-432 solution as that of the aspirated intracystic fluid, but not exceeding 0·2 mg OK-432, was injected. On the other hand, when the lesions consisted mainly of many small cystic masses and aspiration of the fluid was difficult or impossible, OK-432 solution was injected into the lesion at a few sites until the administered OK-432 solution resulted in slight expansion of the tumour, up to a maximum of 0·1 mg OK-432 at one injection. OK-432 was injected again 3–4 weeks later if the initial dose was considered insufficient for the treatment of these lesions.

Results

Complete regression was observed in eight patients within 2–3 months and an additional injection of OK-432 was required in three of eight patients (*Table 1*). No recurrence was observed during the follow-up periods of 6 months to 1 year and 2 months. In the remaining patient, marked regression in tumour size was noted following the two courses of OK-432 therapy.

Fever of 2–3 days' duration and slight tenderness and swelling of the cystic hygroma continuing for 3–4 days after the injection were noted, but serious side-effects were not encountered. Local inflammatory reaction did not cause any damage to the overlying skin and did not lead to scar formation.

Discussion

OK-432 is produced by incubating the culture of the low virulent Su strain of type III, group A *Streptococcus pyogenes* of human origin with penicillin G potassium followed by lyophilization of the incubation mixture, which results in the complete disappearance of streptolysin S-producing ability[9]. OK-432 is routinely administered intradermally or intravenously, at a dosage of 0·1–0·5 mg at one injection 1–3 times a week for a long duration in adults and children[10]. This potent biological response modifier augments various cytotoxic effector cells and induces immunostimulatory cytokines[9,11,15]. The LD_{50} values of OK-432 in mice and rats after subcutaneous, intraperitoneal or intravenous administration were 238 mg/kg and 431 mg/kg, 125 mg/kg and 175 mg/kg or 25 mg/kg and 25 mg/kg, respectively[9].

Torisu *et al.*[12] and Nagao[13] reported that intracavitary injection of OK-432 in patients with malignant effusion in the pleural or peritoneal cavity results in disappearance of effusion in approximately 90 per cent of patients. Torisu *et al.* speculate that the mechanism of fluid disappearance from the peritoneal cavity involves activation of the complement system in the ascitic fluid by OK-432, resulting in the release of anaphylatoxins and chemotactic factors which cause inflammation of the peritoneum; consequently fluid production is decreased because of damage to endothelial cells in the peritoneum and deposition of fibrotic tissue[12].

The basic mechanism of the therapeutic effects of sclerosing therapy for cystic hygroma was thought to mainly involve inflammatory changes due to the reaction of chemical stimulation to tissues, which causes the sclerosis and cicatrical contraction of the lymphangioma[6,16]. Based on these findings and the observation that OK-432 has no major side-effects[17], we extended this OK-432 therapy to the treatment of cystic hygroma in children. Cystic hygromas are multilobular, multiocular cystic masses composed of many individual cysts varying from 1 mm to 5 cm or more in diameter[1].

As shown in *Table 1*, complete regression was noted in eight patients and marked regression, which was expected to result in cure of hygroma, was noted in one patient after a very short interval. An additional injection of OK-432 was required in cases 1, 4, 7 and 8. No recurrence was noted in any of the patients that showed complete regression of the lesions during the follow-up periods of 6 months to 1 year and 2 months.

Kinmonth reported two cases of cystic hygromas in the neck which were successfully treated by injection of Ethamolin (Glaxo) (ethanolamine oleate BNF) into each cyst after aspiration of intracystic fluid, but there is a risk of the injected fluid entering the thoracic duct and subsequently the blood circulation[18]. Bleomycin has been used with favourable results[5,6,8]; however, a major concern has been the unpredictable, and occasionally fatal, development of pulmonary fibrosis, hence its abandonment as an alternative sclerosant. With OK-432 therapy, we noted only transient fever lasting 2–3 days, which could be reduced with antipyretics, and an inflammatory reaction of 3–4 days' duration at the injection site in all cases immediately after the injection of OK-432. The inflmmatory reaction did not cause

Table 1 *Results of sclerosing therapy with OK-432 for cystic hygroma*

Case	Age	Sex	Site	Treatment (dose and times)	Results	Remarks
1.	4 months	F	Shoulder	OK-432 (0·1 mg × 1; 0·2 mg × 1)	Cured	No surgery[14]
2.	4 years 11 months	F	Neck	OK-432 (0·04 mg × 1)	Cured	No surgery
3.	9 months	M	Submaxilla	OK-432 (0·1 mg × 1)	Cured	No surgery
4.	1 year 10 months	M	Auricle	OK-432 (0·01 mg × 2)	Cured	No surgery
5.	2 years 10 months	F	Neck	OK-432 (0·04 mg × 1)	Cured	No surgery
6.	10 months	M	Abdomen and thigh	Surgery (IE × 3)—OK-432 (0·1 mg × 1)	Cured	Secondary to IE
7.	2 years 5 months	M	Retroperitoneum to thigh	Surgery (IE × 3)—OK-432 (0·2 mg × 2)	Improved	Secondary to IE
8.	1 year 6 months	F	Face	OK-432 (0·15 mg × 2)	Cured	No surgery
9.	14 years	F	Neck	OK-432 (0·1 mg × 1)	Cured	No surgery

IE, incomplete excision

any damage to the overlying skin and did not lead to scar formation. We think that this inflammatory reaction is important, since the inflammation and eventual destruction of the cyst lining is responsible for the ultimate cure.

Our results indicate that sclerosing therapy with a single injection of OK-432 is useful for the treatment of these lesions.

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Intussusception in children 5–15 years of age

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Twenty cases of intussusception in children between the ages of 5 and 15 years were compared with intussusception in infancy and early childhood. They accounted for 18·5 per cent of all 108 children treated for intussusception in two large hospitals from 1964 to 1984. Diagnosis of intussusception was delayed, probably due to an unusual presentation. Fifty-five per cent had a definite predisposing factor precipitating the intussusception and 45 per cent had a small bowel intussusception, which warranted early surgical intervention. In the absence of contra-indications no child should be disqualified from an attempt at hydrostatic reduction. After hydrostatic reduction careful follow-up is required to exclude an organic lesion, possibly by a small bowel follow-through meal. Surgery is indicated after hydrostatic reduction in case of chronically recurrent abdominal complaints.

Keywords: Intussusception, children

Intussusception is the commonest cause of small bowel obstruction in children between the ages of 2 months and 5 years. After the first year the incidence gradually declines. Intussusception is uncommon in children at the age of 5 years or over[1–4].

Whereas intussusception in children under the age of 5 years has often been the subject of studies, little attention has been paid to intussusception in children 5–15 years of age. This prompted the authors to examine the records of all 108 children treated for intussusception over a 20-year period in our two hospitals serving a district of 300 000 people. Children between the ages of 5 and 15 years represented 18·5 per cent of the total.

In the records of the 20 patients in this age group we found several striking differences when compared with recently published reports of large series which considered predominantly children under the age of 5 years[4–9].

Patients and methods

The records of all 108 patients under the age of 15, admitted to the Department of General Surgery of the St. Canisius-Wilhelmina Hospital in Nijmegen or to the Paediatric Surgical Centre of the St. Radboud Hospital of the Catholic University of Nijmegen from 1964 to 1984 in whom the clinical diagnosis of intussusception was supported either by radiological evidence or by laparotomy, were subject to a retrospective study. Twenty patients were between the ages of 5 and 15 years. The records of the paediatrician and/or (paediatric) surgeon as well as all available X-rays were reviewed.

Results

The mean age was 8½ years for the 10 male and 10 female patients. Nine had an intussusception of the enteric type (jejunojejunal or ileo-ileal), one was an ileo-ileocolic intussusception, and the rest were of the ileo-(caeco-)colic type. In only two cases was the classic triad of colicky pain, vomiting and rectal bleeding present (*Table 1*). Six children showed only one symptom: pain or vomiting. A palpable abdominal mass was present in four of five patients whose sole complaint was abdominal pain; nine of the eleven children with colicky pain and vomiting but without bloody stools had a palpable mass. In only five patients was the diagnosis made within 24 h after the onset of symptoms, while eight had had symptoms for more than 3 days. With the exclusion of three chronic intussusceptions the correct diagnosis was reached on an average of 3 days after the onset of symptoms. Five children had had recurrent abdominal complaints for a period of 8, 8, 6, 6 and 3 months respectively. In 14 the diagnosis was made clinically and by barium enema examination. Six cases were diagnosed at laparotomy.

Treatment

An attempt at hydrostatic reduction was performed in 11 children and was successful in 6. In three of the five cases of failed hydrostatic reduction a predisposing factor precipitating intussusception was found. Gangrene necessitated a partial resection of the small bowel in the fourth patient. During laparotomy in the fifth child the intussusception was found to have undergone spontaneous reduction.

Laparotomy was performed on 14 patients. One intussusception reduced spontaneously, and manual reduction was performed in 13 cases. Enterotomy was carried out for excision of a polyp (2), for biopsy of marked lymphoid hyperplasia (1) and for biopsy of an ulcer in the caecum (1). Partial jejunal resection (1) was performed because of a tumour which turned out to be a fibroid polyp. On four occasions partial resection of the ileum was required because of non-viable bowel.

Out of the group of 14 children undergoing laparotomy a definite predisposing factor precipitating the intussusception was present in 11 cases (*Table 2*). In all three children with chronic intussusception and in four of the five with recurrent abdominal complaints laparotomy revealed an organic lesion.

Complications and recurrences

During and after hydrostatic reduction no complications occurred. One patient had a recurrence 2 days after laborious hydrostatic reduction of an ileocolic intussusception. Again hydrostatic reduction was performed. During a follow-up period of 7 years the patient had no further trouble. In another child small bowel obstruction due to adhesions warranted relaparotomy after partial ileal resection. There were no recurrences after surgical treatment.

Table 1 *Clinical features*

Symptoms	Number of cases ($n=20$)	Cases with abdominal mass
Pain	5	4
Pain + vomiting	11	9
Vomiting	1	—
Pain + rectal bleeding	1	—
Pain, vomiting + rectal bleeding	2	1

Table 2 *Predisposing factors in 20 cases of intussusception in children 5–15 years of age*

Aetiological factor	Number of cases
Meckel's diverticulum	2
Peutz–Jeghers syndrome	2
Appendiceal stump	1
Hamartoma	1
Fibroid polyp	1
Lymphoid hyperplasia	1
Mucoviscoidosis	1
Severe nephrotic syndrome	1
Postoperative phase after correction hernia hiatus oesophagi	1
Total	11

Discussion

In recently published reports from large children's hospitals the 5–15 age group account for less than 5 per cent[2–4], compared with 18·5 per cent in this series. This relatively high percentage is probably not due to a higher incidence but to a lower incidence of intussusception in infancy and early childhood. We calculated a low incidence of intussusception of 1·1 per 1000 live births compared with incidences of 1·57 to over 4 per 1000 live births reported in a review by Ravitch[1]. Per year we saw one patient between the ages of 5 and 15 years with intussusception. Intussusception is thus an uncommon cause of abdominal complaints in the older age group[10].

The striking difference in presentation is conducive to delay in diagnosis[10]. In children under the age of 5 years the classic triad of pain, vomiting and rectal bleeding is present in about 20–50 per cent[7,11]. At school age we found it to be less frequent (10 per cent). Abdominal pain (in 75–94 per cent) and vomiting (in 63–92 per cent) are by far the most common presenting features in intussusception[1,5–9]. In infants and younger children rectal bleeding is a rather frequent symptom (46–67 per cent)[4–8]. We found rectal bleeding to be rare. In contrast an abdominal mass, usually found in 50–85 per cent[1,4–8], is a significant diagnostic finding. An abdominal mass was present in 14 of our patients. To avoid delay in diagnosis we recommend barium enema examination in any child who might possibly have an intussusception. In experienced hands ultrasonography can be most helpful in evaluating atypical cases[12].

In infancy and childhood intussusception is due to an organic lesion in 2–12 per cent[1,4–9], while in the older child there is a much higher incidence[3,6–8]. Intussusception due to organic lesions is more difficult to reduce hydrostatically[9]. The enteric or ileo-ileocolic type is more common in the older child[8,9], and this type is difficult to treat by hydrostatic reduction[9]. It is the general experience that there is a higher failure of hydrostatic reduction in older children[10]. Eklöf (1980) and Jennings (1984) reported a more than 20 per cent lower success rate of hydrostatic reduction compared with their overall success rate[2,3]. In our view older children can be treated by hydrostatic reduction provided there is adequate follow-up and an organic lesion of the small bowel has been excluded. In the case of chronically recurrent abdominal complaints surgery is indicated.

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Thrombosis of the superior mesenteric vein

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Four patients under 45 years old presented with small bowel infarction secondary to superior mesenteric venous thrombosis. Diagnosis was not made pre-operatively in three patients and delay to operation of over 4 days occurred in two patients. In each case infarcted bowel was resected and a primary anastomosis fashioned. A further resection of infarcted small bowel was necessary in three patients. Each patient was discharged on long-term warfarin therapy. Two patients required permanent total parenteral nutrition, one of whom died of liver failure at one year. The remaining patients remain well.

Keywords: Superior mesenteric vein thrombosis

Thrombosis of the superior mesenteric vein or its tributaries is a rare cause of small bowel infarction which can affect young adults[1,2]. Diagnosis is difficult and may be missed at laparotomy. Early recognition and treatment is important as thrombosis and intestinal infarction may progress unless involved bowel and mesentery are resected[3] and anticoagulation therapy promptly instituted when appropriate[4,5]. We report the clinical features and outcome of four young adults with small bowel infarction secondary to superior mesenteric venous thrombosis.

Patients

A long history of non-specific abdominal pain and lack of marked physical signs were characteristic of each patient (*Table 1*). Apart from a raised white cell count and platelet count in patients 3 and 4, routine investigations were unhelpful. As a result, operation in two cases was delayed until 4 and 5 days after admission. The decision to operate was based on clinical grounds alone in patients 1, 2 and 4. In patient 3 gastroscopy revealed lower oesophageal varices and a superior mesenteric arteriogram subsequently demonstrated no capillary perfusion or venous phase in part of the proximal jejunum.

At operation no mechanical cause was found to explain the small bowel necrosis. The mesentery was oedematous and on cutting thrombus extruded from the veins. The arterial supply to the affected bowel was normal. Resection of necrotic bowel and primary anastomosis of apparently healthy bowel was performed in three cases. In patient 4 the thrombotic process affected the entire small bowel and caecum to varying degrees. Rather than perform total small bowel and caecal resection only infarcted bowel was resected and the patient immediately heparinized. Histology in each case confirmed the diagnosis of mesenteric venous thrombosis.

Within 24 hours, further resection of necrotic small bowel was necessary in patient 1, after which he was heparinized and long-term total parenteral nutrition initiated. Apart from an early brachiocephalic vein thrombosis which necessitated resiting of the feeding line recovery was uneventful. Diagnosis was not made at laparotomy in patient 2, consequently heparinization was delayed for 2 days when histology was available. Despite anticoagulation progressive small bowel infarction necessitated further resection at 4 days. After this operation the patient made an uneventful recovery.

Patient 3 was heparinized immediately after operation. Eleven days later he developed a small bowel obstruction which was relieved by division of adhesions. Abdominal pain necessitated a third operation 9 days later. At operation the remaining small bowel was necrotic and had to be resected; a duodenostomy was fashioned and the ileocaecal stump oversewn. Long-term total parenteral nutrition was started after the second operation. As in patient 2, the central venous line had to be resited because of thrombosis of the subclavian vein. Progressive jaundice developed after the initial admission and liver biopsy showed cholestasis which was ascribed to portal hypertension secondary to portal vein thrombosis. One year later he died of liver failure. Although the likelihood of reoperation was anticipated in patient 4 this proved unnecessary.

In each patient prothrombin time and thrombin time were normal. Antithrombin III levels were normal in patients 1 and 4. In patient 3 the antithrombin III level determined 8 days after the second operation was 60 per cent of the normal value. The initially high platelet counts in patients 3 and 4 returned to normal after operation and were thus considered a response to sepsis rather than a myeloproliferative disorder. All patients were discharged on long-term warfarin therapy.

Discussion

Intestinal infarction secondary to mesenteric venous thrombosis as distinct from arterial occlusion was described in 1935[6,7]. It is a rare condition accounting for 0·01–0·06 per cent of all cases of intestinal infarction[1,2] and 5–15 per cent of cases without mechanical bowel obstruction[1,2,8–11].

Several conditions may be associated with mesenteric venous thrombosis. These include portal hypertension (usually secondary to cirrhosis or congestive splenomegaly)[1,7,12], bacterial peritonitis[7,12,13], abdominal trauma[14,15], splenectomy[12,16,17] and malignant disease[12,13]. In patient 4 established portal vein thrombosis was obviously a major aetiological factor in the development of superior mesenteric venous thrombosis. Extensive investigations, including clotting studies, performed when she initially presented with oesophageal varices were normal, and because of the risk of bleeding anticoagulant therapy was not instituted. Possibly she has a primary undefined thrombostatic disorder.

Early reports coined the term primary or spontaneous mesenteric venous thrombosis to describe patients in whom no predisposing cause was identified[4,5,13]. In these patients a history of peripheral venous thrombosis and migratory thrombophlebitis is not unusual[4].

In recent years the importance of antithrombin III deficiency in the development of mesenteric venous occlusion has been recognized[18]. It is likely that some cases previously labelled primary mesenteric venous thrombosis are in fact due to antithrombin III deficiency. Patient 1 probably represents a spontaneous thrombosis although an unrecognized thrombostatic defect cannot be excluded. By contrast, in patient 3 antithrombin III deficiency is likely. The antithrombin III activity measured 8 days postoperatively was 60 per cent of normal at which level there is an increasing likelihood of spontaneous thrombosis[19]. The physiological reduction in antithrombin III levels following an operation usually returns to normal by 7 days[20].

Venous thrombosis leading to bowel infarction is a slow event. As a result approximately 50 per cent of patients have a history exceeding 5 days[4], as occurred in our patients. Characteristically the pain is disproportionate to the physical findings[21]. Because mesenteric venous thrombosis is

Table 1 *Clinical features of four patients with superior mesenteric venous thrombosis*

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	39	28	39	43
Sex	Male	Male	Male	Female
Length of history (days)	14	6	6	21
Relevant medical history	Deep vein thrombosis	Nil	Nil	Portal vein thrombosis, bleeding oesophageal varices transected
Symptoms and signs	Abdominal pain, distension, reduced bowel sounds	Abdominal pain, vomiting, reduced bowel sounds	Abdominal pain, weight loss	Abdominal pain, vomiting, splenomegaly
Delay to operation (days)	1	5	4	3
Hg (g/dl)	16·9	13·4	11·7	12·7
WCC × 10^9/l	9·1	12·9	24·2	19·3
Platelets × 10^9/l	382·0	425·0	>875.0	588
Antithrombin III	Normal	Not done	60% of normal	Normal
Operations	1. Ileal resection—primary anastomosis 2. At 1 day jejunal resection—primary anastomosis	1. Jejunal resection—primary anastomosis 2. At 4 days jejunal and ileal resection—primary anastomosis	1. Jejunal resection—primary anastomosis 2. At 11 days division of adhesions 3. At 21 days resection of remaining small bowel duodenostomy	Jejunal and ileal resections—primary anastomoses
Outcome	Home parenteral nutrition Well at 3 years	Well at 3 months	Home parenteral nutrition Died of liver failure at 1 year	Well at 3 months

uncommon and the diagnosis is rarely made pre-operatively there is often an in-hospital delay of up to 3–5 days before operation[22]. Even at operation the diagnosis may be overlooked by the inexperienced surgeon, as occurred in patient 2.

No specific laboratory investigations exist for the diagnosis of mesenteric venous thrombosis. An increase in haematocrit level and white cell count is usual. Plain abdominal X-ray is abnormal in 50–75 per cent of cases usually demonstrating an ileus, bowel wall thickening, mucosal irregularity or ascites[23–25]. Superior mesenteric arteriography will show slow or absent blood flow and no venous drainage from the affected site[23].

Successful treatment demands early resection of affected small bowel and mesentery to encompass the entire thrombotic process[3]. Primary anastomosis is advocated by some surgeons[3], however recurrent infarction, usually involving the anastomosis, develops in up to 60 per cent of cases and is likely in part to be due to incomplete resection[26]. As a result exteriorization of the bowel ends or second-look laparotomy have been advocated[27]. The experience in this series highlights the need for a radical primary resection and difficulty in determining the extent of the thrombotic process. If a limited length of intestine is affected complete resection can be achieved. However, the entire small bowel may be affected to varying degrees, as in patient 4. In such cases resection of only infarcted bowel and associated mesentery with immediate anticoagulation and acceptance of the possible need for further laparotomy may be appropriate[27]. The problems of total parenteral nutrition, particularly major vein thrombosis, also justify a more conservative approach. Occasionally, thrombectomy has been successful when large proximal veins are involved[28,29]

Postoperative anticoagulation is recommended in patients with spontaneous mesenteric venous thrombosis or in whom a coagulopathy is discovered[4,5]. In such cases anticoagulation should probably be continued indefinitely. In secondary cases the safety of anticoagulation will depend on the primary disease process. All patients in whom there is no obvious primary cause for thrombosis require detailed evaluation of their clotting function.

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Case report

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Serious hazard of plastic coding tape on surgical instruments

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Many hospital sterile supply departments mark surgical instruments with bands of coloured plastic tape to facilitate the making up of sets for regularly performed operations. We report a serious hazard of this practice.

Case report

An elective tracheostomy was performed uneventfully on a patient requiring long-term ventilatory support. Four days postoperatively, brisk bleeding occurred through the tracheostomy tube. The tube was changed but bleeding continued and signs of respiratory distress developed. There were diminished breath sounds over the left lung field and a chest X-ray showed complete opacification of the left lung. Fibre-optic bronchoscopy was performed; fresh blood and clots were aspirated from the left main bronchus but no obvious bleeding site was found. A repeat chest X-ray showed considerable clearing of the left lung field.

Two days later, the patient became hypoxic and the chest X-ray again showed complete opacification of the left lung. Fibre-optic bronchoscopy was repeated and blood clot was found obstructing the left main bronchus. The clot could not adequately be removed via the fibre-optic instrument and rigid bronchoscopy was performed under general anaesthesia. After removal of the clot, a foreign body was seen to be eroding the mucosa on the medial wall of the left main bronchus. The foreign body was removed and found to be a 12 × 6 mm piece of coloured plastic coding tape of the kind used to mark surgical instruments. The remainder of the bronchial tree was normal. Subsequently, the chest X-ray again cleared. There was no further bleeding.

Discussion

It must be assumed that the piece of coloured plastic tape entered the bronchial tree during the tracheostomy since this was the only time that marked surgical instruments were used.

Although no precise figures are available, discussion with colleagues suggests that the use of coloured plastic tape to mark sets of surgical instruments is becoming more widespread. There is a previous report of a piece of instrument marking tape being left in a surgical wound causing postoperative infection[1]. In view of these complications we recommend that the need for such marking be carefully considered, and avoided if possible. Where marking tapes are thought to be strictly necessary, they should be checked to be both present and intact on every instrument at the beginning and end of each operation with exactly the same rigour as that currently applied to swab and instrument counts.

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The ischaemic leg as a source of complement activation

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Complement activation before and after surgical resection was studied in 40 patients with ischaemic legs (17 with acute and 23 with chronic ischaemia). Plasma anaphylatoxin concentrations (C3a and C5a) and anaphylatoxin inhibitor (AI) activity were studied pre-operatively, and 1 h, 24 h and 1 week postoperatively. Increased plasma anaphylatoxin concentrations were found pre-operatively. Anaphylatoxin levels in plasma had returned to normal one week postoperatively. Patients with acute ischaemia had higher plasma C3a and C5a pre-operatively and during the first 24 h postoperatively than patients with chronic ischaemia. Anaphylatoxins increase vascular permeability, smooth muscle contraction and histamine release from mast cells. Their enhanced activity might be one of the explanations for respiratory, hepatic and renal insufficiency before surgical resection in patients with extensive ischaemia.

Keywords: Anaphylatoxins, anaphylatoxin inhibitor, complement, ischaemia, ischaemic limbs

Patients with ischaemic limbs are prone to develop respiratory and circulatory complications[1]. Ischaemia can be suspected when there are alterations in the acid–base balance, lactate and purine metabolites[2].

Complement is activated by foreign tissue, by tissue changed by thermal or mechanical injury or by hypoperfusion[3–7] (*Figure 1*). Anaphylatoxins (C3a and C5a) are formed in the blood from the C3 and C5 molecules when complement is activated[8]. In human serum the anaphylatoxins are rapidly inactivated by an enzyme with carboxypeptidase activity. *In vitro* tests indicate that C3a and C5a are inactivated within 2 min by sera containing the anaphylatoxin inhibitor (AI)[9]. The serum carboxypeptidase cleaves off the C-terminal arginine residue from the anaphylatoxins[9]. Thereafter, the $C5a_{desArg}$ molecule only retains part of the anaphylatoxin activity in its new form[10]. C3a and C5a are polypeptides with molecular weights of 9000 and 8300 daltons respectively[11]. They increase vascular permeability, and trigger smooth muscle contraction and release of histamine from mast cells and basophils[12–15]. Anaphylatoxins may also impair cardiac function[16]. Important interactions exist among the complement, kinin, coagulation and fibrinolytic systems[17]. They include common activating enzymes and inhibitors and overlapping effects on the cellular elements[18]. Both C3a and C5a release histamine from mast cells and proteases and peroxidases from leucocytes[13,19]. Anaphylatoxins stimulate biosynthesis of the arachidonic products leukotrienes and prostaglandins[20]. Neutrophils and macrophages activated by C5a may also cause production of oxygen-free radicals[21]. Prolonged elevation of plasma anaphylatoxins is associated with development of multisystem organ failure[22]. C5a induces polymorphonuclear neutrophil chemotaxis[10,23]. Complement-induced granulocyte aggregation has also been proposed as a major factor in the aetiology of the adult respiratory distress syndrome[24].

The aim of this work was to determine whether complement is activated and anaphylatoxins are formed in patients with extensive ischaemia of the leg. We also wanted to find out whether there is any correlation between altered plasma C3a and C5a concentrations and impaired pulmonary, hepatic and renal function in these patients.

Patients and methods

Patients

Forty consecutive patients (mean age 74·4 years, range 54–90 years) with ischaemic limbs were studied. Seventeen patients had acute and twenty-three chronic ischaemia. Acute ischaemia was defined as promptly interrupted arterial blood flow or development of ischaemia after failure of embolectomi. Eleven of seventeen patients with acute ischaemia had ischaemia above the knee and the amputation was performed above the knee joint. Four of twenty-three patients with chronic ischaemia had nonviable tissue above the knee. In these four patients the amputation was performed above the knee. The mean operation time was 42 min for the whole group and the mean perioperative bleeding was 175 ml.

All patients were anaesthetized with intradural tetracaine injection (Tetracain 65–75 mg). Two of the patients died within 24 h postoperatively, in circulatory shock. These two patients were excluded. None of the patients was treated with corticosteroids. No patient had positive blood cultures during hospital stay.

Methods

Venous blood was drawn pre-operatively and 1 h, 24 h and 7 days postoperatively. The samples were immediately placed in tubes with EDTA (ethylene diamine tetraacetic acid) for plasma or without EDTA for serum. The tubes were centrifuged to remove the cells and the plasma or serum samples were immediately frozen and kept at −80°C until the C3a and C5a concentrations and the inhibitor activity were determined. The plasma concentrations of C3a and C5a antigens were determined with a radioimmunoassay method described by Wagner and Hugli[25]. The concentrations of these components in our standard plasma did not differ from those in a known reference plasma. AI activity in the serum was analysed according to Corbin[26]. All quantitations were performed in duplicate. The standard deviation of 40 duplicate determinations of C3a and C5a were less than 6 per cent of the mean, and of AI less than 8 per cent of the mean.

Bilirubin, ASAT (aspartate aminotransferase), ALAT (alanine aminotransferase), creatinine, alveolar–arterial oxygen difference ($(A–a)O_2$ diff.), and the leucocyte and platelet counts were determined by standard methods.

Statistics

Mean values and standard errors of the mean were calculated by standard methods. Fisher's test was used for comparison of groups[27]. Differences are described as significant when $P < 0·05$.

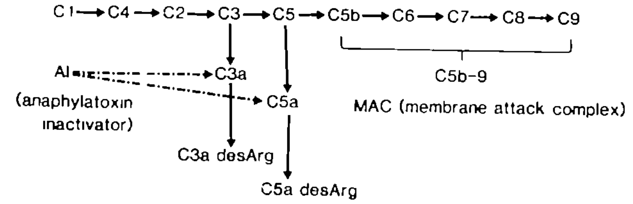

Figure 1 *Activation of the complement cascade*

Results

Complement variables (C3a, C5a and AI) and clinical variables (bilirubin, ASAT, ALAT, creatinine, (A–a)O_2 diff., leucocyte and platelet counts) are given in *Tables 1* and *2*.

C3a was increased in patients with chronic ischaemia of the limb ($P<0{\cdot}001$). Plasma C5a was, however, not increased in these patients. Twenty-four hours postoperatively C3a was lower than pre-operatively and one hour postoperatively in patients with chronic ischaemia ($P<0{\cdot}05$). One week postoperatively plasma C3a levels were within the normal range.

Plasma concentrations of C3a and C5a were increased pre-operatively in patients with acute ischaemia ($P<0{\cdot}001$, $P<0{\cdot}05$ respectively). Plasma C3a and C5a were still higher than normal 1 and 24 h postoperatively in patients with acute ischaemia ($P<0{\cdot}001$, $P<0{\cdot}05$ respectively) but returned to normal within one week after the operation (*Table 1*).

Plasma C3a and C5a were higher in patients with acute ischaemia before and during the first hour after operation than in patients with chronic ischaemia ($P<0{\cdot}05$).

No significant difference in AI activity was observed between the two groups (*Table 1*).

Patients with acute ischaemia had increased bilirubin, creatinine, and (A–a)O_2 diff. pre-operatively compared with patients with non-viable tissue below the knee ($P>0{\cdot}05$). These variables returned to normal within one week after resection of ischaemic tissue. No significant pulmonary, hepatic, or renal dysfunction was found in the group with chronic ischaemia. Patients with extensive ischaemia also had an increased oxygen requirement pre-operatively and during the first day postoperatively ($P>0{\cdot}05$). No significant alterations in ASAT and ALAT concentrations were found in either of the groups (*Table 2*).

Pre-operatively and during the first week postoperatively, both groups of patients had an increased leucocyte count ($P<0{\cdot}05$). The platelet count was within the normal range in both groups.

Table 1 *Complement variables in patients with ischaemic limbs*

	C3a (ng/ml)	C5a (ng/ml)	AI (units ml)
Normal values (range)	156 (108–204)	5 (<10)	392 (318–466)
Chronic ischaemia ($n=23$)			
Pre-operatively	397±37***	7·5±2·3*	404±41
1 h postoperatively	381±42*	7·0±1·7*	411±56
24 h postoperatively	291±32*†	5·8±1·5*	447±82
7 days postoperatively	232±23†	5·3±1·0	465±62
Acute ischaemia ($n=17$)			
Pre-operatively	630±53***	12·1±3·2*	374±78
1 h postoperatively	527±43*	14·2±4·0*	393±43
24 h postoperatively	434±41*†	12·2±3·1*	465±72
7 days postoperatively	218±27†††	5·4±1·1†	462±72

Values are mean±s.e.m.
Significances
Difference between the two groups: *$P<0{\cdot}05$, **$P<0{\cdot}01$, ***$P<0{\cdot}001$
Difference within the groups, compared with the pre-operative values: †$P<0{\cdot}05$, ††$P<0{\cdot}01$, †††$P<0{\cdot}001$

Discussion

Complement is activated and anaphylatoxins are released in patients with ischaemic limbs. A correlation exists between the volume of non-viable tissue and the degree of complement activation.

The mortality rates for above-knee amputations are much higher than for below-knee amputations[28]. In addition to a disturbed acid–base balance and increased lactate levels, extensive anaphylatoxin formation might be one reason for the increased mortality in above-knee amputees. Investigators have suggested that hypoxic muscle releases cardiopressant metabolites[29]. Earlier studies have also demonstrated that soft tissue injury and infusion of homogenized autologous muscle tissue initiate complement activation[30,31]. As C3a causes impairment of atrioventricular function, tachycardia, and coronary vasoconstriction, anaphylatoxin release might influence myocardial function in patients with gangrene[16,32].

Patients with acute ischaemia also showed signs of slightly impaired pulmonary, hepatic and renal functions. Earlier studies have shown a correlation between anaphylatoxin generation and impaired function of these organs[22]. In this study, however, none of the patients developed more than mild multisystem organ failure. After resection of ischaemic tissue, the plasma anaphylatoxins returned to normal within one week. One reason why these patients did not develop severe organ dysfunction might be lower plasma C3a and C5a concentrations and a shorter duration of increased concentrations compared with those observed in earlier studies. The two patients who died within 24 h after the operation had extensive ischaemia above the knee. They had very high plasma anaphylatoxin levels pre-operatively and postoperatively. In three patients, a second resection had to be done. After the first resection, plasma C3a returned to the normal range but it increased when the patients developed a new gangrene. After the second operation C3a returned to normal again (*Figure 2*). In these three patients, no changes in the C5a levels were observed.

Only a few patients with acute ischaemia had high C5a concentrations. Earlier studies have, however, shown both

Table 2 *Haematological variables in patients with ischaemic limbs*

	Bilirubin (μmol/l)	ASAT (μmol/l)	ALAT (μmol/l)	Creatinine (μmol/l)	(A–a)O_2-diff. (kPa)	Leucocyte count (cells/mm^3 × 10^3)	Platelet count (cells/mm^3 × 10^3)
Normal values	3·4–21	<0·7	<0·7	50–115	2·6–7·8	4·0–10·0	150–400
Chronic ischaemia ($n=23$)							
Pre-operatively	8·9±1·2*	0·7±0·2	0·6±0·2	93±16*	4·4±1·4*	11·6±2·5	337±32
24 h postoperatively	9·1±1·2*	0·8±0·1	0·7±0·1	95±19	4·8±1·6	10·6±3·2	392±51
7 days postoperatively	9·2±1·4	0·9±0·2	0·6±0·2	78±18	5·3±2·1	12·0±2·7	404±51
Acute ischaemia ($n=17$)							
Pre-operatively	14·6±3·4*	0·9±0·2	0·7±0·2	127±20*	7·7±1·8*	12·3±3·1	313±32
24 h postoperatively	15·0±4·0*	0·8±0·2	0·6±0·1	126±28	7·0±2·3	14·1±3·5	398±32
7 days postoperatively	7·6±1·3†	0·8±0·1	0·6±0·1	112±17*	5·1±1·8†	12·7±3·3	430±77

Values are mean±s.e.m.
Significances
Difference between the two groups: *$P<0{\cdot}05$, **$P<0{\cdot}01$, ***$P<0{\cdot}001$
Difference within the groups, compared with the pre-operative value: †$P<0{\cdot}05$, ††$P<0{\cdot}01$, †††$P<0{\cdot}001$

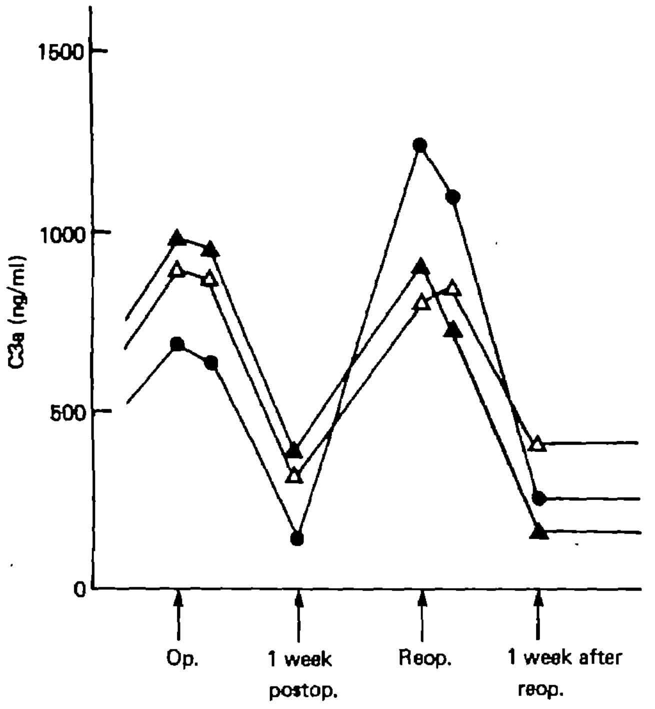

Figure 2 *Plasma C3a in three patients with ischaemic limbs before, during and after amputation and reamputation*

reduced C3 and reduced C5 concentrations in these patients, which indicates that conversion of C3 and C5 has occurred[33]. $C5a_{desArg}$ is with great avidity internalized and degraded by neutrophils. This elimination might mask an increased formation of C5a in patients with extensive ischaemia. Despite a very short turnover time for the anaphylatoxins, the plasma concentrations are elevated 24 h postoperatively. Release by anaphylatoxins of histamine, prostaglandins, leukotrienes and production of oxygen-free radicals by complement activated leucocytes may explain the different effects observed when complement-split products appear in plasma. Tissue damage associated with acute inflammation that is complement dependent may therefore be related to generation of oxygen-free radicals[34]. Prostaglandins affect for example the pulmonary and central haemodynamics as well as respiration[35,36].

There are pharmacological ways to influence complement activation and results of increased anaphylatoxin activity. High doses of methylprednisolone reduce neutrophil aggregation and inhibit toxic oxygen radical production by these cells[37]. In patients with ischaemic limbs, however, the underlying disease has to be treated. All the patients studied were treated by resection of ischaemic tissue. The anaphylatoxins returned from elevated to normal concentrations in plasma within one week after resection of nonviable tissue.

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Case report

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Mondor's disease as a presenting symptom of breast cancer

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Mondor's disease is a rare and relatively little known clinical entity. Clinical features include sudden development of localized pain in the breast, followed by palpable and visible, tender, cordlike, branching cutaneous grooves. This clinical picture was first described by Fagge in 1869[1]. Subsequently, sporadic cases were reported up to 1939 when Henri Mondor, a French surgeon, described the disease that now bears his name[2]. The disease involves phlebitis and periphlebitis of the lateral thoracic or thoraco-epigastric vein occurring mostly in women between the ages of 21 and 55 years. Men are affected as well and comprise about one-third of the cases[3]. Aetiology is not known although it may be related to recent local trauma, muscular strain, minor operative procedures on the breast and pre-existing febrile episodes[4]. There seems to be no relationship to systemic disease or cancer[5].

We report a case of Mondor's disease as a presenting feature of primary breast cancer.

Case report

A married woman, 54 years old, was seen in the breast clinic with a 2-week history of pain and cordlike swelling in the upper and outer quadrant of the left breast. She reported that neither injury nor unusual activity took place before her condition. On examination, there were two inflamed, tender cords, one extending along the anterior axillary fold to about the sixth rib on the lateral aspect of the left breast, and the second extending from the mid-clavicular point along the inner quadrants of the same breast. The superficial veins around the cords were more prominent than corresponding veins on the opposite side. At first examination, no discrete lump of the breast was palpated. However, a mammogram was requested and the patient reviewed 10 days later. On this occasion the inflammation and pain had improved and the cords were less apparent. The mammogram demonstrated an unequivocal cancer at this site. Histology was confirmed by local excision of the lump and treatment completed by axillary dissection and postoperative radiotherapy.

Discussion

The presence of breast cancer in this patient with Mondor's disease is an unusual association. Miller *et al.* have reported a case in which the early manifestation of recurrent axillary metastasis from breast cancer was ipsilateral thrombophlebitis of the breast[6]. In this patient pain from the superficial thrombophlebitis of the breast led to examination and identification of Mondor's disease and, subsequently, to the diagnosis of breast cancer. Although the mammographic findings in Mondor's disease have not been well-documented, they are generally considered to be inconclusive[7]. Mammography in this case proved to be very helpful in revealing breast cancer which otherwise might have been missed. Whether the two conditions were unrelated or directly associated is a matter for conjecture. This case reinforces the advice for routine mammography in all women over the age of 50 with breast symptoms.

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Use of a lipid containing medium chain triglycerides in patients receiving TPN: a randomized prospective trial

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Lipid emulsions which contain long chain triglycerides (LCTs) provide a valuable energy source for patients requiring total parenteral nutrition (TPN). We have investigated the use of a new lipid emulsion containing both long and medium chain triglycerides (MCTs) in a randomized prospective trial. Sixty patients received TPN including 500 ml of either 20 per cent Lipofundin S (LCT) or Lipofundin 10 per cent MCT/10 per cent LCT for at least 6 days. Patients with renal or hepatic impairment, or major trauma, were excluded from the study. The MCT/LCT emulsion was found to be as safe and as effective a source of calories as LCT but the differences in metabolic parameters did not differ significantly between the two groups of patients. A lipid emulsion containing MCTs may have important advantages for seriously ill patients, but appears to have no obvious advantages for the majority of patients receiving TPN who are not severely stressed.

Keywords: Parenteral nutrition, medium chain triglycerides

Long chain triglyceride emulsions (LCTs) are a common source of calories in total parenteral nutrition (TPN) regimens. Non-esterified fatty acids released by hydrolysis are used as an energy substrate for many tissues, and are also metabolized to ketones in the liver. These ketone bodies, β-hydroxybutyrate and acetoacetate, are known to be a useful source of energy in ill patients[1]. Ketones are produced in the mitochondria of liver cells, and the transport of long chain fatty acids across the mitochondrial membrane is dependent on an enzyme system requiring carnitine. Carnitine may be depleted in seriously ill patients, and medium chain triglycerides (MCTs) may therefore have advantages for use as a substrate for ketogenesis as their transport is relatively independent of carnitine[2]. An intravenous lipid preparation containing MCTs has recently become available for clinical trials.

A short-term crossover comparison of this intravenous MCT preparation with a LCT emulsion in a small number of patients demonstrated improved ketogenesis and decreased serum triglyceride levels after MCT compared with LCT infusion[3]. Nitrogen balance was also improved, indicating that MCTs may have a better protein-sparing effect. An additional 3-day study comparing MCT/LCT with LCT alone in postoperative patients receiving 5 per cent dextrose infusions but no TPN, did not demonstrate any significant difference in triglyceride or ketone levels[4].

The aim of the present study was to investigate further the metabolic effects of MCT infusion over a longer time period in a larger group of patients receiving standard TPN[5], and to confirm its safety and freedom from adverse effects.

Patients and methods

Seventy-one patients (35 women and 36 men), considered to require standard TPN for a minimum of 6 days, were randomized to receive half their non-nitrogen calories as either 20 per cent LCT (Lipofundin S, B. Braun, Melsungen, FRG) or 10 per cent MCT/10 per cent LCT (B. Braun). The TPN regimen also contained 250 g carbohydrate, 14 g nitrogen as L-amino acids (Aminoplasmal), electrolytes and trace elements (*Table 1*). Patients with cardiac dysrhythmias, renal or hepatic impairment or known abnormalities of lipid metabolism were excluded from the trial. Patients were also excluded if major surgery was planned during the first 3 days on TPN, or if TPN was required immediately after major trauma. Informed consent was obtained from all patients and the study had the approval of the Central Oxford Ethics Committee.

The triglyceride infusions were given over 8 h. On days 1, 3, 6 and 10 of the study the plasma triglyceride and ketone concentrations were measured before the start of the lipid infusion, and on days 1 and 6 the measurements were repeated 6 h later. Plasma triglycerides were measured enzymatically (Sigma Chemical Co.), and the concentration of acetoacetate and β-hydroxybutyrate were measured using β-hydroxybutyrate dehydrogenase[6].

Routine biochemical and liver function tests were measured daily on a monitor parallel analyser, and haematological indices measured on a Coulter S-plus analyser. Nitrogen losses were calculated from the 24 h urinary urea excretion which was measured daily.

Statistical analysis of the data was performed using the Mann–Whitney *U* test.

Results

Of the 71 patients entered into the trial, 11 were excluded from the analysis because they failed to complete the minimum period of 6 days on TPN. The results obtained from 60 patients were analysed. Thirty-one patients received 20 per cent LCT and twenty-nine patients received 10 per cent MCT/10 per cent LCT. The two groups were well matched for age (LCT: median 51 years, range 21–81 years; MCT/LCT: median 50 years, range 22–84 years), and duration of feeding (LCT: median 12·4 days, range 6–25 days; MCT/LCT: median 14 days, range 6–41 days). The main indication for feeding in both groups was inflammatory bowel disease and its complications (*Table 2*). There was no discernible clinical difference between the patients in each trial group, and the basal nutritional indices were similar (*Table 3*).

Prior to TPN, both groups of patients had similar mild ketonaemia as a consequence of starvation and endogenous lipolysis (LCT: median 121 μmol/l, range 0–2470 μmol/l; MCT/LCT: median 104 μmol/l, range 3–1940 μmol/l) (*Figure 1*). Ketone levels were reduced threefold by the TPN and the pre-lipid infusion levels on days 3, 6 and 10 were similar in both groups (day 3 LCT: median 26 μmol/l, range 1–31 μmol/l; MCT/LCT: median 27 μmol/l, range 6–116 μmol/l; day 10

This paper is based on a presentation to the Surgical Research Society in January 1986

Table 1 *Standard electrolytes, vitamins and trace elements*

				Vitamin supplements (alternate days i and ii) in addition to 15 mg folic acid per day and 10 ml Vitlipid Adult (KabiVitum) per week			
Electrolytes (per day)		Trace elements (per week)		(i) Multibionta (Merck, FRG)		(ii) Parentrovite 1 and 2 (Bencard, UK)	
Sodium	100 mmol	Zinc	10 mg	Vitamin A	10 000 units	Vitamin B_1	250 mg
Potassium	100 mmol	Copper	4 mg	Vitamin B_1	50 mg	Vitamin B_2	4 mg
Calcium	7 mmol	Manganese	1 mg	Vitamin B_2	10 mg	Vitamin B_6	50 mg
Magnesium	9 mmol	Chromium	40 μg	Vitamin B_6	15 mg	Nicotinamide	160 mg
Zinc	0·2 mmol			Nicotinamide	100 mg	Vitamin C	500 mg
Chloride	110 mmol			Vitamin C	500 mg		
Phosphate	30 mmol			Vitamin E	5 mg		

Table 2 *The main indications for parenteral nutrition in those patients receiving either LCTs or MCT/LCTs*

	Numbers of patients receiving:	
	LCT	MCT/LCT
Inflammatory bowel disease	9	12
Sepsis	5	4
Postoperative complications	6	3
Trauma	1	1
Gastrointestinal fistulae	0	1
Other conditions	10	8

Table 3 *Prefeeding nutritional indices for patients receiving either LCTs or MCT/LCTs*

	LCT	MCT/LCT
Weight (kg)	56·90±14·80	55·50±11·68
Grip strength (kg)	28·23±6·77	25·08±9·08
Maximum arm circumference (cm)	24·77±4·77	23·66±3·89
Skin-fold thickness (mm)	7·91±3·99	6·68±2·52
Albumin (g/l)	31·36±5·00	29·25±4·12
Haemoglobin (g/dl)	11·88±1·99	12·23±2.01

Values are mean ± s.d. There were no significant differences between the two groups

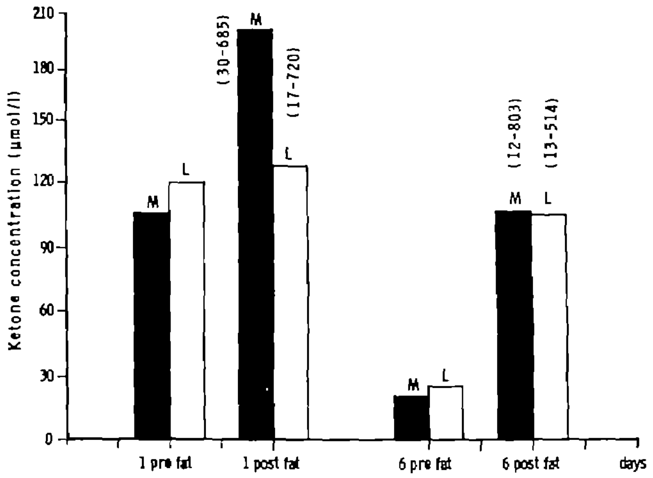

Figure 1 *Plasma ketone concentration before lipid administration and after 6 h infusion in patients receiving MCT/LCTs* ■ *or LCT* □ *(median values with range)*

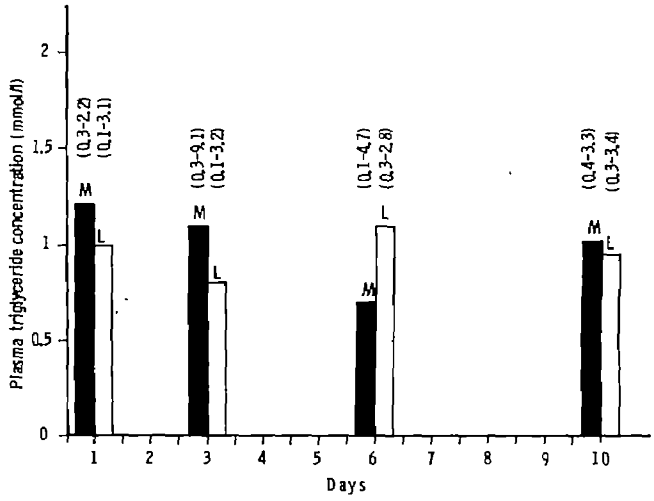

Figure 2 *Comparison of plasma triglyceride levels before lipid infusion in patients receiving MCT/LCTs* ■ *or LCTs* □ *(median values with range)*

LCT: median 24 μmol/l, range 0–286 μmol/l; MCT/LCT: median 26 μmol/l, range 7–73 μmol/l) (*Figure 1*). Basal triglyceride levels were also similar in both groups for each of the study days (*Figure 2*).

The rise in plasma ketones after 6 h of lipid infusion was not statistically different between the two groups on either day 1 or 6, although on day 1 there was a trend towards a greater increase in those patients receiving MCT/LCT (the difference in median values being 0·099 with 95 per cent confidence limits of −0·043, 0·304) (*Figure 1*).

Plasma triglyceride levels predictably rose during the lipid infusion but the magnitude of this increase in the two groups was similar (the difference between the median values after triglyceride infusion of the MCT/LCT and LCT groups on day 1 being 0·48 with 95 per cent confidence limits of −0·89, 2·48 and on day 6 was 0·83 with 95 per cent confidence limits of −2·0, 3·1). The levels varied enormously between individuals (on the first day, after 6 h infusion, LCT: median 2·8 mmol/l, range 1·7–9·7 mmol/l; MCT/LCT: median 4·5 mmol/l, range 1·3–9·1 mmol/l). Similar baseline levels on subsequent days indicated no marked impairment of lipid clearance in either group (*Figure 2*).

Urinary nitrogen excretion was similar in both groups, the cumulative median nitrogen balances for 1 week being 17·46 g (range −14·54 to 32·36) for those receiving MCT/LCT, and 19·32 g (range −11·35 to 35·41) for those receiving LCT. There were no significant differences in the haemoglobin, white cell or platelet counts on any day between the two groups of patients, and liver function test results were also similar (*Table 4*).

Discussion

The aim of TPN is to sustain health, minimize muscle protein breakdown and maintain a positive nitrogen balance. An amino acid solution is therefore provided with a source of calories. As

Table 4 *Results of routine liver function test performed before the start of TPN and on day 10 of parenteral feeding for patients receiving LCTs or MCT/LCTs*

Parameter	Before TPN		Day 10 TPN	
	MCT/LCT	LCT	MCT/LCT	LCT
Albumin (g/l)	28·7±0·9	28·7±1·5	28·9±1·2	30·0±1·2
Bilirubin (μmol/l)	14·2±3·0	16·7±4·2	12·4±2·4	26·1±8·9
AST (units/l)	26·9±4·0	48·3±2·1	36·4±7·0	33·3±6·9
Alkaline phosphatase (units/l)	229±38	193±15	429±91	243±23

Values are mean±s.e.m.
AST, aspartate aminotransferase

lipid emulsions have been shown to promote nitrogen retention to the same extent as glucose, while having other metabolic and clinical advantages[7–9], many centres, therefore, now use glucose together with lipid to provide the non-nitrogen calories.

The lipid emulsions in common use contain LCTs. These products have been extensively studied and their advantages and disadvantages documented[10–12]. Recently a MCT-containing emulsion has been developed. MCTs have theoretical advantages over LCTs as the transport of the medium chain fatty acids across the mitochondrial membrane following intracytoplasmic esterification is relatively independent of carnitine[2]. MCT infusions should be associated with greater increases in plasma ketone bodies compared with LCT infusions, and triglyceride levels should be correspondingly lower, reflecting more efficient triglyceride utilization. In the present study, however, we found no significant differences in these parameters, or in the clinical outcome, between those patients receiving the MCT/LCT emulsion compared with those receiving LCTs alone.

Although there is some evidence that carnitine stores may become depleted in the seriously ill, suggesting that endogenous production of carnitine may be insufficient for some patients receiving long-term parenteral nutrition[13,14], there are only few reports of patients on TPN developing a clinical syndrome that could be related to carnitine deficiency[15]. In the present study carnitine levels were not measured, but the lack of a distinct metabolic advantage for patients receiving MCTs implies that the majority of patients receiving routine TPN are not carnitine deficient.

In the short crossover trial previously performed in this centre we reported greater increases in plasma ketone levels and an associated improvement in nitrogen balance when the patients were receiving MCT/LCT compared with when they received LCTs alone. Although in the present study a similar trend of improved ketogenesis was demonstrated in patients receiving MCT/LCT this difference did not reach statistical significance. Various factors may have contributed to the disparity between the two studies. In Oxford, 75 per cent of patients requiring TPN are only mildly stressed and malnourished and are parenterally fed using a standard regimen containing 250 g carbohydrate, 14 g nitrogen and 500 ml of a 20 per cent triglyceride emulsion[5], and nearly all patients are maintained in positive nitrogen balance. The crossover study included patients who were severely ill (two of whom died), and who were more likely to have reduced carnitine stores. This may explain the higher levels of ketone bodies which occurred when these ill patients were infused with MCT/LCT, and it is well recognized that ketone infusion can improve the nitrogen balance[1], which was also observed in the crossover study.

The trial designs may have contributed to the differences in results between the two studies. Patients vary considerably in their ability to metabolize fat emulsions, which is reflected in the variance in plasma ketone and triglyceride levels both before and after fat infusion. In addition, lipid emulsions on occasion may be difficult to regulate and inadvertent changes in the infusion rates may be a further cause of variability in the plasma concentrations of the lipid metabolites. Although the same variability existed in the crossover trial, the patients acted as their own controls and therefore more subtle changes in the metabolic measurements could be detected. A randomized trial does not have this advantage, therefore moderate differences are masked by the wide individual variation, and the numbers of patients needed to demonstrate these differences would be in the order of 200–300.

Although we have not demonstrated any clinical advantages of MCT/LCT in patients who are not severely stressed, this study is important as it has shown that these emulsions are safe and satisfactory for routine use with no apparent clinical or biochemical complications in patients receiving 500 ml daily for a minimum of 6 days. However, if the lipid preparation containing MCT/LCT is more expensive than that with LCTs alone it will be important to identify patients for whom MCTs have a particular benefit.

Acknowledgements

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Case report

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Record number of gallstones

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A case is reported of a patient whose gallbladder contained 23 530 stones. This is believed to be a record. The gallbladder had undergone malignant change.

Case report

An 85-year-old woman presented with severe colicky central abdominal pain of 24 h duration. On examination there were signs of intestinal obstruction and an indistinct, non-tender mass was palpable in the right upper quadrant.

At laparotomy (K.W.M.) a localized carcinoma of the caecum was found which was causing small bowel obstruction. The mass in the right hypochondrium was a hugely distended gallbladder packed with gallstones. There was thinning of the gallbladder wall but no evidence of inflammatory change. A right hemicolectomy and cholecystectomy were performed and the gallbladder emptied of stones which filled two kidney dishes (*Figure 1*). Painstaking counting revealed a total of 23 530 gallstones ranging in size from 1·0 mm to 1·5 cm in diameter. Histology of the gallbladder showed changes of carcinoma *in situ* with a frank invasive poorly differentiated carcinoma at one site. Elsewhere, there was mild chronic inflammatory fibrosis.

Discussion

The 23 530 gallstones counted in this case appears to be a record. They now reside in the Pathology Museum of St. Thomas' Hospital Medical School. Thudichum[1] states that Paré described 1000 in a single gallbladder, Meckel upwards of 3000 and Naunyn 5000; Harding Rains[2] states that Schackrev, who counted 14 000, holds the record. No greater number appears to have been published.

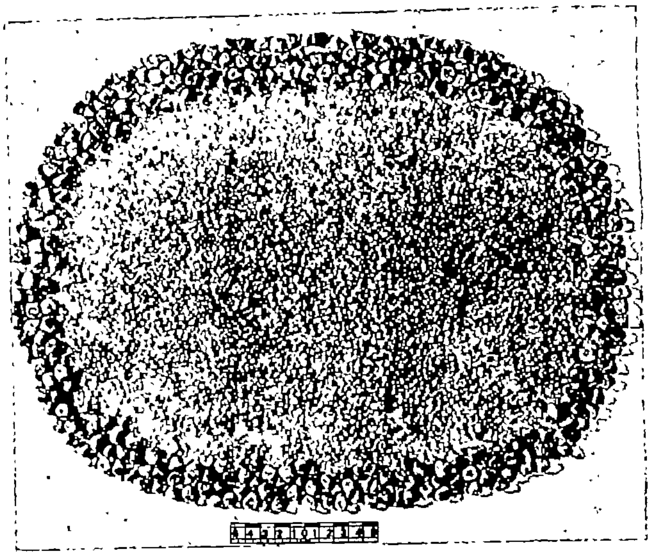

Figure 1 *23 530 discrete gallstones removed from a single gallbladder*

Dr Knowles, consultant pathologist at Chichester, has counted the gallstones contained in over 2400 gallbladders excised by his surgical colleagues over the last 15 years. Of these, 28 contained more than 1000 gallstones, the largest number being 17 306 (C. H. R. Knowles, unpublished results.)

Most people enjoy collecting and surgeons are not immune. This case history is presented as a surgical and pathological 'collector's piece'.

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Review

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Potential impact of immunobiotechnology on cancer therapy

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Genetic engineering techniques allow large scale production of substances generated during the immune response and these may have therapeutic value by modifying the biological response to cancer.

For most non-lymphoid tumours arising from epithelial organs the standard therapeutic triad of surgery, radiotherapy and chemotherapy appears to be approaching the limits of its potential for the successful eradication of advanced stages of the disease. This is particularly so for carcinomas of the gastrointestinal tract, lung, kidney and malignant melanoma, and clearly alternative avenues require exploration. Over the past 5 years there has been an explosion of laboratory observations in the field of immunobiotechnology which have now entered, or are about to enter, clinical application. It seems appropriate to review some of these lines of research which are almost certain to influence our overall view of the management of tumour bearing patients over the next 10 years. Most surgeons are aware of the development of monoclonal antibodies against molecules present on the surfaces of some human tumour cells and of the potential of these reagents for imaging and treatment. It is not my intention to discuss these here since recent workshops have reviewed the current status of this approach[1,2]. Rather, I wish to draw attention to some of the developments which, together with the use of genetic engineering techniques for the large scale production of certain molecules generated during an immune response, have resulted in the concept of a new 'fourth modality' of treatment which, by general agreement, has been termed 'biological response modification'. Before attempting to describe the current clinical status of this approach it may be of value to describe briefly those components of the immune response which are of relevance to anti-cancer therapy.

Current concepts of the immunological response

An encounter with foreign antigen initiates a cascade of cellular and molecular interactions which are summarized in a very simplified form in *Figure 1*. It will be recalled that there are two distinct categories of lymphocyte, namely those processed in pre-natal life via the thymus and hence known as T cells, and those which do not undergo any thymic processing and are termed B cells. B cells are normally stimulated to proliferate by antigen under the influence of various growth factors, and ultimately mature into specific antibody-producing plasma cells. This proliferative and maturation phase occurs clonally, i.e. the progeny of one antigen-stimulated B cell undergoes multiple cell divisions to produce a group of identical plasma cells all of which produce a single identical specific antibody against the antigen in question. The fusion of one of these progeny with an immortal myeloma cell is the basis of monoclonal antibody production. T lymphocytes can also expand clonally and are divided into sub-classes such as helper T cells, cytotoxic T cells (generated in response to allografts and modified 'self' antigens) and suppressor T lymphocytes which act as a negative feedback mechanism on the immune response. The existence of a third category of lymphocyte which does not appear to express the characteristics of either T or B cells is also acknowledged; it is referred to as a null cell. These represent only a small proportion of the total circulating lymphocyte population, but they are important because they include the large granular lymphocytes (LGLs) which exert naturally occurring cellular cytoxocity against certain tumour cells. These LGLs are known as natural killer (NK) cells and they will be referred to frequently in this review.

Antigen is 'processed' by activated macrophages which present this processed antigen to helper T cells. These latter possess receptors for the antigen and also receptors for a soluble mediator known as interleukin 1 (IL 1) which is released by activated macrophages. The binding of processed antigen and IL 1 by their respective receptors on helper T lymphocytes causes these to produce and secrete several other soluble factors (lymphokines) such as γ-interferon (γ-IFN) and interleukin 2 (IL 2). IL 2 is an indispensable growth factor for the development of cytotoxic T cells (CTLs) and is bound to a specific receptor on the surface of antigen-primed CTL precursors (CTLp). The simultaneous binding of antigen and IL 2 by CTLp causes their clonal proliferation with the generation of large number of CTLs which have the capacity to kill any cells bearing the stimulating antigen. This is the mechanism responsible for acute graft rejection and the elimination of virally or chemically altered 'self' antigens (e.g. influenza, dinitrochlorobenzene). CTLs with specificity for autologous tumour cells have been described in patients suffering from carcinoma of the lung[3], gastrointestinal tract[4] and malignant melanoma[5]. Thus it is not necessary to postulate the existence of specific tumour 'antigens' on the surface of tumour cells, since their acquisition of modified self antigens would serve equally well to elicit a cellular cytotoxic response.

NK cells also exist as non-cytotoxic precursors which may be activated to become cytotoxic NK cells under the influence of several growth factors such as[6] the interferons and IL 2. NK cells are so-called because they do not require prior sensitization *in vivo* but are already spontaneously cytotoxic to a variety of *in vitro* maintained tumour cell lines. Their presence in human peripheral blood can readily be measured and a wide range of values is found in healthy individuals. They are generally credited with the role of immunosurveillance against virally transformed and malignant cells[7], but their *in vitro* targets are usually cells of lymphoid origin, there being little evidence that they are spontaneously cytotoxic to epithelial tumour cells. However, although not cytotoxic towards primary non-lymphoid cell lines *in vitro*, there is now substantial evidence that NK cells may become activated *in vivo* against metastatic tumour cells, particularly those NK cells which reside in certain organs of election for epithelial metastases such as the liver and lungs[8,9].

The above account briefly describes some physiological components of the immune response which have relevance to certain aspects of anti-tumour therapy, although it is not intended to imply that they are necessarily always activated as a 'host reaction' during the growth of a spontaneously arising solid tumour. Several other anti-tumour cytotoxic phenomena

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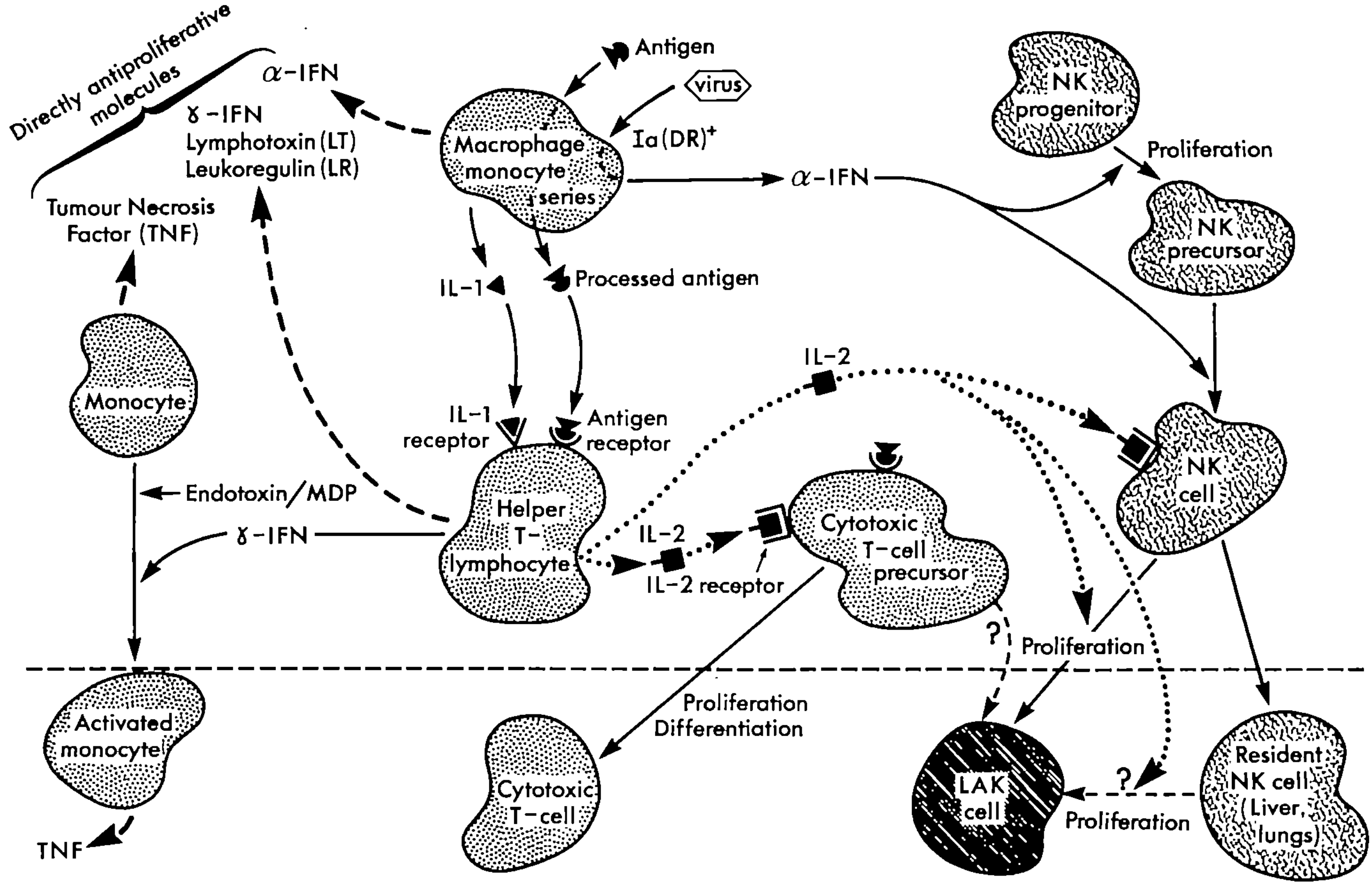

Figure 1 *Diagrammatic representation of cellular and molecular interactions resulting in responses of potential clinical value (see text). Cells with anti-tumour cytotoxic capacities are indicated below the horizontal dotted line. Molecules with direct anti-proliferative effects on tumour cells are indicated in the top left-hand corner. Abbreviations: IL-1, interleukin 1; IL-2, interleukin 2; α-IFN, α-interferon; γ-IFN, γ-interferon; TNF, tumour necrosis factor; Ia, immune associated gene product; NK, natural killer; LAK, lymphokine activated killer*

can be elicited experimentally which may prove to be of therapeutic interest. Thus γ-IFN (but not α- or β-IFNs) can activate macrophages *in vitro* to become cytotoxic towards tumour cells but this appears to require a priming cofactor such as bacterial endotoxin or muramyl dipeptide in order to be effective[10]. Such cytotoxic macrophages have been described in patients with colorectal cancer[11] and are potential candidates for adoptive cellular immunotherapy in such patients. Of greater importance is the discovery that resting lymphocytes cultured for 3 or 4 days in the presence of high doses of IL 2 become highly cytotoxic towards tumour cells of a variety of origins, including autologous tumour, when these lymphokine-activated killer (LAK) cells are generated from the lymphocytes of tumour-bearing patients[12,13].

It will be apparent that the cellular immune responses which are of potential value in the tumour-bearing patient are derived from cellular precursors which require activation *in vivo* and/or *in vitro* if adoptive cellular immunotherapy is contemplated. To this end large quantities of biologically derived materials such as IL 2 or interferons may be required, these quantities perhaps greatly exceeding those which might be obtained by the isolation and purification of these materials from supernatants of human cells stimulated to release the appropriate molecule in deep bulk culture. Fortunately, molecular biologists have been able to provide vast quantities of these molecules using sophisticated techniques of genetic engineering. Space does not permit a detailed description of these methods but the way in which, for example, genetically engineered human IL 2 is manufactured is summarized in *Figure 2*. It is now possible to derive the peptide sequence of any given protein. Knowledge of this sequence permits one to derive the nucleotide sequence in human DNA which codes for that particular protein and, using the molecular biologist's 'scalpels' (known as restriction

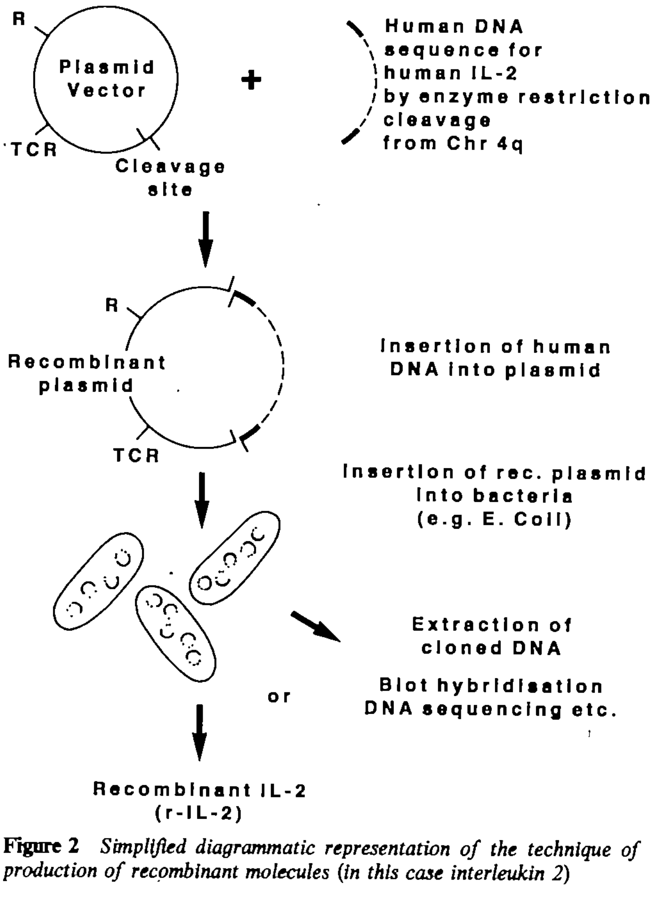
R
Plasmid Vector
TCR
Cleavage site
+
Human DNA sequence for human IL-2 by enzyme restriction cleavage from Chr 4q
R
Recombinant plasmid
TCR
Insertion of human DNA into plasmid
Insertion of rec. plasmid into bacteria (e.g. E. Coli)
Extraction of cloned DNA
Blot hybridisation
DNA sequencing etc.
or
Recombinant IL-2
(r-IL-2)

Figure 2 *Simplified diagrammatic representation of the technique of production of recombinant molecules (in this case interleukin 2)*

Table 1 *Source and action of interferons*

	Source	Action
α-IFN	Monocytes Lymphoblasts Recombinant	Directly tumoristatic Activates NK cells
β-IFN	Fibroblasts	Activates NK cells
γ-IFN	Lymphocytes Recombinant	Activates NK cells Activates monocytes Activates LAK cells Directly tumoristatic

enzymes), human DNA can be dissected until the particular strand which codes for the protein in question is obtained. These DNA strands can be inserted into mammalian cells or bacteria which can then respond to this human DNA signal and produce large quantities of the protein for which it codes. The most common manner in which this is accomplished is to 'suture' the human strand into bacterial plasmids (ring-shaped strands of DNA found in *Escherichia coli* which only code for one or two proteins) again using restriction enzymes. The human gene thus combined into the bacterial plasmid (hence the term recombinant gene) is then re-inserted into the *E. coli* which, being essentially a protein factory, proliferates rapidly in culture and manufactures vast quantities of the human protein (recombinant protein) coded for by the human gene. A number of human proteins have now been produced in this fashion including human growth hormone[14] and insulin[15]. Of particular interest in the present context, however, is the fact that a number of human proteins with immunological activities such as IL 2 and some subclasses of interferons have been made available in large quantities by this technology.

The clinical exploitation of biological responses and their modifiers in human cancer therapy

Interferons

Interferons are the archetypal biological response modifier with *in vitro* and *in vivo* properties which have potential in cancer therapy. They comprise a family of proteins derived from several sources and divided into three distinct groups termed α, β and γ interferons. Their principal origins and properties are summarized in *Table 1*. These proteins have been peptide and DNA sequenced and the corresponding recombinant molecules have been characterized and purified for clinical use[16–18]. These agents have anti-viral, anti-proliferative and immunoregulatory properties but much of their interest lies in their capacity to increase NK activity *in vitro*[19] and *in vivo*[20,21]. It will be recalled that organ-specific resident NK cells are capable of killing epithelial metastases. Thus it was envisaged that the interferons would be effective not only through their direct antiproliferative effects on tumour cells but also by activation of these host biological responses with tumoricidal activity. Unfortunately the augmentation of peripheral blood NK activity seen during the first 2 weeks of treatment is not maintained during continued therapy and the subsequent decline in NK activity has been confirmed in a number of clinical studies[22–24]. Regrettably the failure to maintain the augmented biological response is paralleled by very low response rates of most advanced solid tumours to interferon therapy alone[24].

For example, Kirkwood[25] observed only 4 partial or complete remissions in 23 malignant melanoma patients treated with 10–50 Munits m^{-2} day^{-1} of recombinant α_2-IFN (r-α_2-IFN) and Quesada[26] observed only 4 partial responses amongst 15 hypernephroma patients treated with the same agent. Similarly only 3 of 20 patients with advanced colorectal cancer showed any evidence of response to continuous or cyclical r-α_2-IFN therapy[27] although 7 of 17 patients with carcinoma of the breast were reported by Gutterman's group[28] to respond to natural, partially purified, human α-IFN of leucocyte origin Preliminary reports of the use of human recombinant γ-IFN in patients with a similar spectrum of tumour origins do not, at first sight, appear to be any more encouraging[29,30].

It is evident therefore that initially the human recombinant interferons were not the oncological 'magic bullet' they were hoped to be, although of course many of these phase I clinical studies were performed in patients with very advanced disease. However, more promising results appear to be emerging when they are combined with other drugs. For example, Hersey's group in Australia have claimed a 50 per cent response rate in 36 patients with disseminated melanoma when r-α_2-IFN was combined with darcarbazine[31]. Interestingly, half of the responders underwent complete remission. Synergistic effects have also been claimed when r-α_2-IFN is combined with Adriamycin in the treatment of patients with non-lymphoid solid organ tumours including pancreatic cancer[32].

A recurring theme in many studies of the use of interferons appears to be that many of the patients whose tumours respond undergo treatment with relatively low-dose interferon whereas the high doses do not seem to provide any additional benefit and indeed some reports imply that acceleration of disease may occur[33]. Similar effects are seen with the cellular cytotoxic responses, NK and monocyte antitumour cytotoxicity apparently being impaired by administration of high doses of IFN whereas low doses induce a more consistent increase in these activities[24]. These observations suggest that unlike chemotherapeutic agents, 'more' may not be 'better' in the case of biological response modifiers. Clearly we still have much to learn about the use of these agents; for example, whether interferons can be used in the perioperative period to reverse the depression of NK activity which we have reported to occur consistently following surgery[34]. This is potentially a vulnerable period for the patient when tumour cells may be displaced either into the systemic and portal circulations and when augmented anti-tumour scavenging may well be critical in the control of metastasis. Can combinations of interferons produce synergistic effects without augmenting their toxicity? What effects do low doses of interferons have on other important components of the endogenous host defences? It is clear that after the early waning of enthusiasm for the use of these molecules an element of optimism is returning as more detailed information on the dosages and effects of the recombinant interferons begins to accrue.

Interleukin 2

As can be seen in *Figure 1*, IL 2 plays a central and dominant role in the generation of a number of cellular immune events. Not only is it essential for the maturation of cytotoxic T lymphocytes from their precursors but it is also implicated in the maintenance of NK cell function. More recently the development of cytotoxic anti-tumour cells from non-cytotoxic precursors in response to high concentrations of r-IL 2 has been described (LAK cells) and exploited clinically. Thus IL 2 possesses all the attributes of a classical biological response modifier without a direct antiproliferative effect on tumour cells.

The principal source of IL 2 production is the helper T lymphocyte although small amounts of this molecule are detectable in NK cells and cytotoxic T cells[35]. The gene which codes for IL 2 is present on chromosome 4q and again, following the elucidation of the sequence of its 150 or so amino acids, the gene has been cloned[36] and the recombinant molecule manufactured (r-IL 2). This material has been extensively investigated with a view to its clinical use in oncology, the initial aims of this approach being to augment the maturation and generation of endogenous cytotoxic lymphocytes in tumour-bearing patients. Some rationale for this treatment is provided by the finding that patients suffering from advanced stages of most tumours exhibit impaired cell-mediated immunological responses[37,38]. This is particularly so in patients with gastrointestinal cancer[39,40] and recently we have shown[41] this to be attributable to an intrinsic defect in the helper T cell production of IL 2. Accordingly, it would appear logical to attempt to remedy this defect by the administration of exogenous IL 2 to patients with advanced disease. In fact, although murine studies have revealed that r-IL 2 does have a marked effect on the generation of CTL *in vivo*, with a reduction in tumour size and sometimes eradication of tumours in IL 2 treated mice[42,43], no encouraging results have emerged from any of the clinical phase I trials of IL 2 used as a single agent in tumour-bearing patients. Indeed, Rosenberg's group in the NIH have reported considerable toxicity of r-IL 2, this consisting of rigors, fever, nausea and vomiting in patients treated with high doses of this material[44]. At present, therefore, there is no evidence that the systemic administration of IL 2 as a single agent in tumour bearing patients has any beneficial effects. However, a number of reports indicate that the local administration of IL 2 at the tumour site may be of value[45,46]. The use of intralesional IL 2 requires further clinical evaluation and it may indeed play a considerable role in future treatment protocols but at present its use seems unlikely to influence disease progression in patients with disseminated tumour.

Lymphokine (IL 2)-activated killer (LAK) cells

In contrast to the results of using IL 2 as a single therapeutic agent, adoptive cellular immunotherapy with autologous lymphocytes stimulated *in vitro* with IL 2 has generated enormous interest. The immunological basis for the clinical application of this treatment has evolved following exhaustive animal studies by Rosenberg and his colleagues at the National Cancer Institute in the United States[47–50]. The principle is that large numbers of the patient's lymphocytes are incubated *in vitro* with high doses of r-IL 2 for several days. During this period precursor cells (mainly NK cells) proliferate and become highly cytotoxic towards allogeneic and autologous tumour cells but not to normal cells[12,13,51]. These lymphokine-activated killer (LAK) cells are then re-infused into the tumour-bearing patient who also receives systemic r-IL 2 intravenously, this apparently being essential to facilitate the continued proliferation and cytotoxic capacity of the LAK cells. The LAK cells localize at secondary tumour sites (especially the liver and lungs) and mediate tumour cell destruction[42,52,53]. The initial report of this therapy by Rosenberg *et al.* was, to say the least, dramatic. Of 25 patients suffering from disseminated carcinomas of the lung, colon, stomach, kidney and oesophagus, as well as melanoma and sarcoma, 11 objective responses were observed including the complete regression of widespread metastases in a melanoma patient[54]. Similar results have been independently reported using a similar regimen of LAK cells generated from autologous spleen in a patient with an unresectable hepatoma[55]. All these patients had massive tumour burdens which had failed to respond to conventional treatment and it is perhaps not surprising that there were recurrences within months of cessation of therapy in some of these patients[56]. However, many melanomas and hypernephromas responded and it is of particular interest to see responses amongst patients with metastatic gastrointestinal cancer.

This exciting and novel treatment requires further intensive investigation before its widespread clinical application. We have found that LAK cell generation is impaired in patients with advanced gastrointestinal cancer[57] and this may well explain why LAK/IL 2 therapy is only partially successful in these patients. Clearly, techniques for augmenting this activity in such patients are required. Impaired LAK cell generation does not seem to be a function of malnutrition since we have been unable to increase LAK cell production by intravenous hyperalimentation[58]. However, LAK cells generated from within tumours themselves appear to be some 10–20 times more potent than those generated from peripheral blood lymphocytes[59]. With the advent of modern lymphocyte cloning techniques such cells may eventually prove to be of considerable importance if their numbers can be sufficiently expanded *in vitro*.

Unfortunately, effective LAK/IL 2 therapy carries several serious side effects. Predominant among these is fluid retention with the development of a widespread capillary leak syndrome and many patients require a period of ventilatory support during therapy. This may be an effect of the r-IL 2 and may perhaps be prevented by corticosteroid administration[60]. Adoptive cellular immunotherapy with LAK cells merits detailed investigation particularly in the presence of smaller tumour loads. Potentially this may represent an important future aspect of adjuvant treatment to surgery for a number of epithelial tumours.

Tumour necrosis factor and lymphotoxins

Tumour necrosis factor and lymphotoxin represent a family of macrophage and lymphocyte products which were originally described following the injection of filtrates from certain Gram negative bacteria into tumour-bearing mice[61]. These tumours underwent haemorrhagic necrosis, this being originally attributed to endotoxin or bacterial lipopolysaccharide (LPS). However, subsequent study has revealed that the tumour necrosis resulted from the activity of a cell-derived soluble factor detectable in the serum of mice treated with *C. parvum*, BCG or endotoxin. Such sera are antileukaemic in mice but neither the necrotizing effect nor the tumour cytotoxicity of this 'tumour necrosis serum' could be explained by endotoxin overspill. It is now appreciated that both effects are mediated by two related molecules, one originally being termed tumour necrosis factor (TNF), the other being called lymphotoxin (LT)[62–64]. TNF is manufactured by macrophages and has a molecular weight of 18·6 kD. LT is generated by lymphocytes and has a molecular weight of 17 kD. Both substances have undergone peptide mapping and this has revealed a 30 per cent homology between them. Because of their similar functional attributes TNF is now termed TNF-α and LT is called TNF-β[65].

TNF-α is almost certainly identical with cachectin, a molecule found in the serum of tumour-bearing mammals[66]. Because of its capacity to suppress lipoprotein lipase in adipocytes this substance may well be responsible for the elevated serum triglycerides and wasting observed in tumour-bearing patients. The physiological role of TNF-α may be to control cellular reactions by regulating the mobilization of energy sources within the cell. However, the mechanism whereby TNF mediates the necrosis of tumours is presently unclear. It has been suggested that TNF exerts a local effect on the tumour vasculature but these molecules are also intimately involved in the cytotoxicity exerted by macrophages, monocytes and possibly also NK cells[67–69]. The production of TNF-α (but not TNF-β) is activated by the contact of NK cells with their cell targets but it seems doubtful that their tumour-killing effect is caused by this molecule[70]. In contrast there is increasing evidence that activated monocytes do exert their antitumour cytotoxicity via TNF-α when activated *in vitro* by LPS[67,69].

Unfortunately, although a potent stimulator of TNF production, LPS is far too toxic for clinical administration. However, recombinant human TNF (r-HuTNF) has recently been generated[71] and preliminary studies commenced in tumour-bearing animals[72]. The intratumoral injection of r-HuTNF into xenografts of human colonic and breast cancers in nude mice has produced well-documented regressions accompanied by peritumoral mononuclear cell infiltration. Intraperitoneal administration alone in these animals had no effect until it was combined with administration of recombinant γ or α interferons[73]. However, human breast cancer xenografts do apparently respond well to intravenous r-HuTNF[74,75]. The role of IFN-γ in augmenting the expression of TNF receptors in human tumours is a fascinating example of the way in which biological response modifiers may be employed logically in order to produce a synergistic effect on the tumour cell *in vivo*[76]. The future of this type of approach clearly depends on the demonstration that such combinations are less toxic than each individual agent alone.

Currently the precise physiological role of TNF in the elimination of aberrant epithelial cells has yet to be defined in the tumour-bearing patient. Recent studies indicate that TNF is a potent activator of polymorphonuclear cell function[77] and it is interesting to speculate that r-HuTNF may have as great a role to play in the management of the septic patient as it does in the patient with malignant disease. The results of the clinical phase 1 studies of r-HuTNF are awaited with interest.

In conclusion, basic biological research into the molecular interactions governing cellular cytotoxic responses against tumours are discovering new effector molecules almost every other day. Some of those described above, as well as some of the more recently described ones such as leukoregulin[78], may well come to have an important role in our future management of the patient with solid-organ malignancy. Others may come to have no identifiable role as anti-cancer agents themselves but serve to support other relevant functions during the course of other treatment protocols. For example, one of the principal side effects of chemotherapy and interferon therapy is leukopenia, and recent evidence indicates that this may be prevented experimentally by the use of recombinant colony stimulating factor (CSF)[79], an important cofactor required for the maturation of many leucocyte precursors. Much may come of the detailed investigation of the use of combinations of biological response modifiers in this fashion, especially in the perioperative period and when the tumour burden is as small as possible. These recent developments in immunobiotechnology may be on the verge of providing us with the reagents to accomplish some progress in improving the long-term prognosis in patients suffering from the more common solid tumours.

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Role of computed tomography in selecting patients for hindquarter amputation

Nine patients with soft tissue sarcomas close to the pelvic girdle and one patient with a primary malignant bone tumour of the pelvis were referred for consideration of hindquarter amputation. Patients were considered unsuitable for hindquarter amputation on clinical grounds if malignant disease infiltrated into the perineum or across the sacro-iliac joint. If disease in the femoral triangle extended above the inguinal ligament the tumour's operability was seriously questioned. Buttock tumours which had passed through the greater sciatic notch to become palpable on pelvic examination were also considered likely to be inoperable. On computed tomographic (CT) examination, tumours were considered inoperable if the psoas muscle was involved above the inguinal ligament, or if malignant disease involved the sacro-iliac joint, sacrum or perineal structures. Soft tissue tumours of the buttock extending significantly through the greater sciatic notch were also considered likely to be inoperable. Five patients thought suitable for hindquarter amputation on clinical assessment had no excluding features on CT; four undergoing hindquarter amputation were proven on histological examination to have good clearance of their tumours. In another patient, considered suitable for hindquarter amputation on clinical grounds, CT suggested that en bloc *wide excision of the tumour was feasible enabling the affected limb to be preserved. Four patients after clinical examination were considered unsuitable for hindquarter amputation and in all cases inoperability was confirmed by CT. CT complements clinical examination and provides an objective and reliable means of selecting patients for hindquarter amputation which should avoid unnecessary surgical exploration.*

Keywords: Hindquarter amputation, computed tomography, sarcoma

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Hindquarter amputation is usually reserved for patients with primary or recurrent soft tissue sarcomas of the proximal thigh or buttock who are not suitable for limb salvage surgery and for patients with primary malignant bone tumours arising from the pelvis or proximal femur[1–3]. The procedure is usually performed only for patients without disseminated disease but is occasionally necessary for the palliation of locally advanced disease to prevent sepsis or severe haemorrhage[1]. In the past patients have been assessed as suitable for curative hindquarter amputation mainly on the basis of clinical examination, with the operability of their tumours being confirmed during preliminary exploratory dissection as described by Gordon-Taylor[4] and Westbury[1]. Our aim was to evaluate the role of computed tomography (CT) as an adjunct to clinical examination in assessing the operability of various tumours before hindquarter amputation.

Patients and methods

Ten patients (eight male) aged 14–77 years with primary or locally recurrent sarcomas of the pelvis, buttock or thigh were referred for consideration of hindquarter amputation. One patient was considered for hindquarter amputation on two occasions; once as case 5 and again 18 months later as case 10. The sites and histological nature of the primary tumours in these patients are shown in *Table 1*. Full clinical examination combined with chest radiography, whole lung tomography, computed chest tomography, isotope bone scans and ultrasound liver scans were used to exclude the presence of disseminated disease. Distant metastases were demonstrated in two patients (cases 10 and 11) of whom one was treated by compartmentectomy (case 11).

Nine patients shown to be free of metastatic disease were assesses for their suitability for potentially curative hindquarter amputation on the basis of careful clinical examination. In addition, one patient with radiological evidence of pulmonary metastases from a synovial sarcoma of the left thigh was considered for palliative hindquarter amputation 18 months after his initial assessment (case 10). Patients were considered unsuitable for hindquarter amputation if, on clinical examination, malignant disease infiltrated into the perineum or across the sacro-iliac joint. If disease in the femoral triangle extended above the inguinal ligament to be palpable in the iliac fossa, and particularly if the psoas

Table 1 *Details of the site and histological nature of the primary tumour in ten patients referred for hindquarter amputation*

Case	Age (years)	Site of tumour	Histology	Metastases
1	56	Left thigh	Liposarcoma	Nil
2	77	Left thigh	Malignant fibrous histiocytoma	Nil
3	14	Right thigh	Fibrosarcoma	Nil
4	25	Left thigh	Neurofibrosarcoma	Nil
5	37	Left thigh	Synovial sarcoma	Nil
6	76	Right thigh	Leiomyosarcoma	Nil
7	42	Left buttock	Myxoid liposarcoma	Nil
8	19	Right buttock	Osteosarcoma	Nil
9	16	Left iliac fossa	Embryonal rhabdomyosarcoma	Nil
10	38	Left thigh	Synovial sarcoma	Lung
11	64	Right thigh	Malignant fibrous histiocytoma	Lung

Case 5 was reassessed 18 months later as case 10

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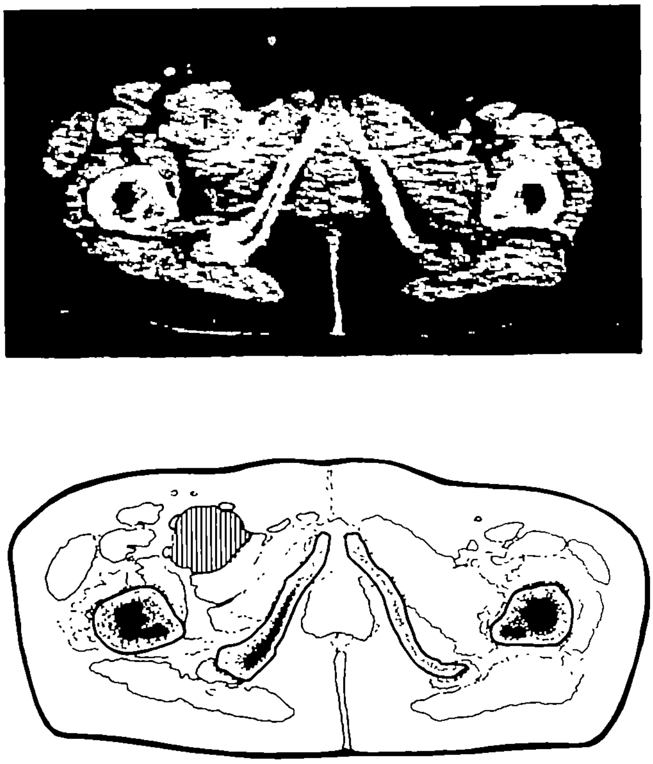

Figure 1 *CT scan of the proximal thighs and diagrammatic representation showing a leiomyosarcoma within the right femoral triangle displacing the superficial and profunda femoris vessels (case 6). The tumour is indicated by T on the scan and by the cross-hatched area on the diagram*

muscle was thought to be involved, the tumour's operability was seriously questioned. Tumours which had passed from the buttock through the greater sciatic notch and which were palpable on digital rectal or vaginal examination were considered likely to be inoperable by hindquarter amputation because of inadequate proximal clearance, particularly of the sciatic nerve roots at the anterior sacral foramina.

Each patient also underwent CT examination of the pelvis and proximal thighs. Tumours were considered inoperable if the psoas muscle was involved by tumour above the inguinal ligament or if malignant disease involved the sacro-iliac joint, sacrum or perineal structures. Similarly, soft tissue sarcomas of the buttock extending significantly through the greater sciatic notch were likely to be inoperable because of inadequate proximal clearance.

Results

Based on the results of careful clinical examination patients were considered either suitable or unsuitable for hindquarter amputation.

Patients suitable for hindquarter amputation

Five patients were thought to be suitable for hindquarter amputation (cases 1–5). Local tumour recurrence following previous excision had occurred in three and all five had received radiotherapy. In each case a well localized tumour mass was shown by CT with no radiological features to suggest that hindquarter amputation was not possible. Except for one patient who refused surgery (case 5) all patients underwent standard hindquarter amputation[1,2] and adequate tumour clearance was subsequently proven histologically.

Another patient (case 6) with a leiomyosarcoma of the right femoral triangle was shown by CT to have a tumour encasing and displacing the common, superficial and profunda femoral vessels and involving the ilio-psoas tendon below the inguinal ligament (*Figure 1*). Although the patient was originally referred for and was considered suitable on clinical grounds for hindquarter amputation, CT suggested that the patient could be treated by *en bloc* wide excision of the tumour and vascular reconstruction which was successfully achieved with preservation of the affected limb[5].

Patients unsuitable for hindquarter amputation

Clinical examination suggested that four patients were unsuitable for hindquarter amputation (cases 7–10). Two of these had extensive buttock tumours. One with a myxoid liposarcoma of the left buttock had disease palpable on the left pelvic side wall on rectal examination (case 7). A second patient with an osteosarcoma of the right ilium had palpable tumour extending into the adjacent sacro-iliac joint posteriorly (case 8). In both cases CT demonstrated tumour spread through the greater sciatic notch into the pelvis confirming the inoperability of the tumours (*Figure 2*). In addition, the patient with the liposarcoma showed evidence of destruction of the left sacral ala (*Figure 3*).

A 16-year-old patient with an embryonal rhabdomyosarcoma of the left iliacus muscle had a large tumour mass

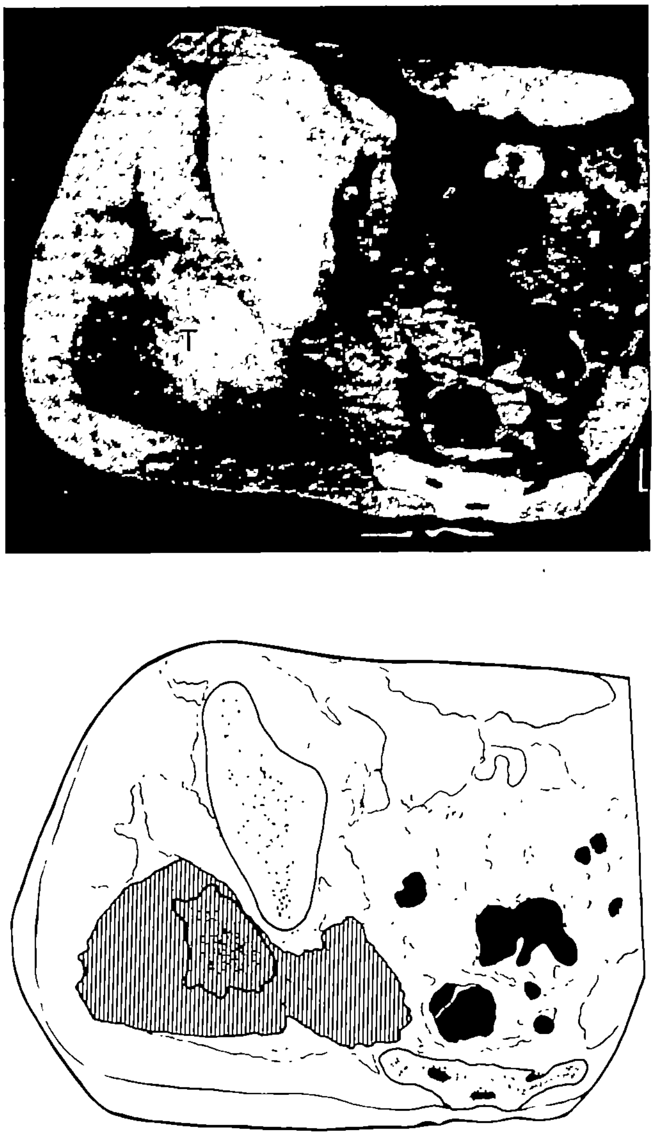

Figure 2 *CT scan of the right side of the pelvis and diagrammatic representation showing an osteosarcoma (T) of the iliac bone dumb-belling through the greater sciatic notch (case 8). Medially the tumour is adjacent to the lateral rectal wall while at its centre is an area of new bone formation indicated by the area of cross-hatching with stippling on the diagram*

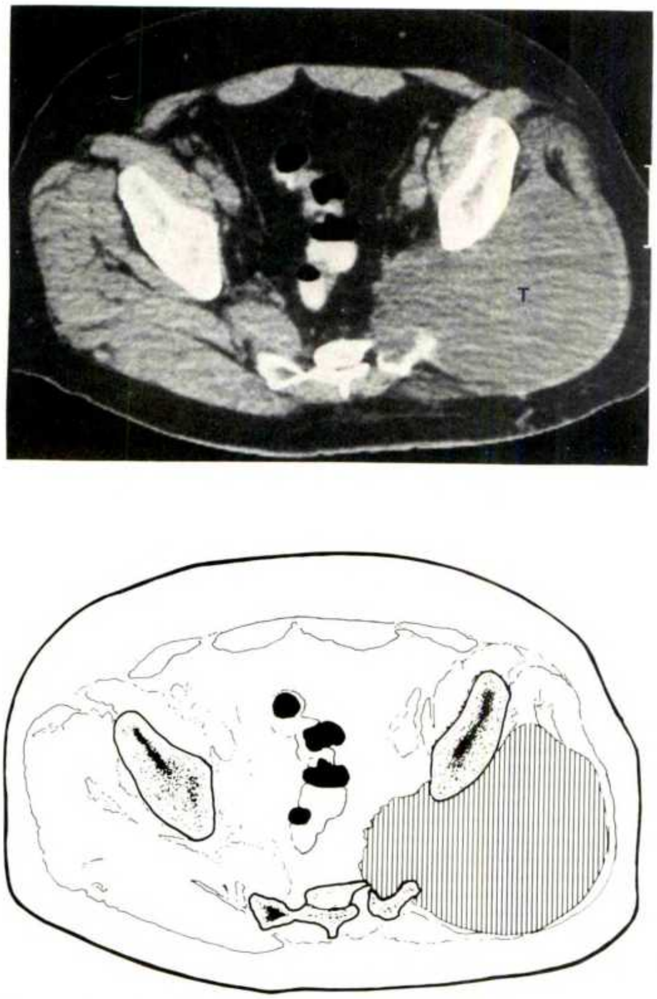

Figure 3 *Pelvic CT scan and diagrammatic representation demonstrating a large myxoid liposarcoma* (T) *of the left buttock extending through the greater sciatic notch and destroying the left sacral ala (case 7)*

visible and palpable in the left iliac fossa (case 9). CT showed extension of tumour across the ipsilateral sacro-iliac joint with involvement of the body of the psoas muscle, confirming its inoperability by hindquarter amputation (*Figure 4*). This patient was treated by intensive chemotherapy for 12 months during which time serial CT scans demonstrated gradual reduction of tumour volume. The residual tumour was irradiated and then resected along with the left iliac wing. The patient remains free of disease 15 months later.

A fourth patient who had refused hindquarter amputation 18 months previously (case 5) presented with pulmonary metastases from a recurrent synovial sarcoma of the left thigh (case 10). Tumour was palpable along the left inferior pubic ramus and on the left lateral pelvic side wall on rectal examination. Invasion of the root of the penis was clearly shown by CT (*Figure 5*). Exploration with a view to palliative ablation was performed because of the threat of possible haemorrhage from a large fungating mass in the left femoral triangle. Hindquarter amputation proved impossible due to extensive spread of tumour into the retropubic space and contralateral side of the pelvis.

Discussion

This study indicates that careful clinical examination by an experienced surgeon can predict the operability of sarcomas by hindquarter amputation. CT confirms the results of clinical examination and should reduce the need for exploratory surgery[1] since it provides objective and reproducible evidence of a tumour's inoperability. In addition, CT may provide supplementary information which identifies those few patients in whom wide tumour excision with limb preservation is possible. This is well illustrated by case 6 in the present study. At all times close co-operation between the surgeon and radiologist is required to obtain the most useful information from CT.

CT is of proven benefit in the management of bone and soft tissue sarcomas demonstrating the local extent of a tumour and predicting its operability and resectability[6-8]. It is also useful in planning complex surgical treatment and fields of radiotherapy. CT is now the investigation of choice in assessing patients with sarcomas, replacing previously used imaging modalities such as radio-isotope bone scintigraphy[9] and arteriography[10]. It is less invasive than arteriography and provides more detailed anatomical information than both these techniques.

CT has other important roles in the management of patients with sarcomas. CT is more accurate than whole lung tomography in the detection of pulmonary metastases[11] and is now an essential pre-operative investigation. It has an important role in detecting local recurrence and is used to assess patients after surgery who have any suspicious clinical features. Also, patients who are selected for primary treatment with chemotherapy or radiotherapy because of large tumour bulk and/or borderline operability and who have an adequate clinical response should be reassessed by CT to determine their suitability for surgical treatment. Case 9 in the present series provides a good example.

The inoperability of the two buttock tumours in this series relates to the extent of their local spread and not primarily to

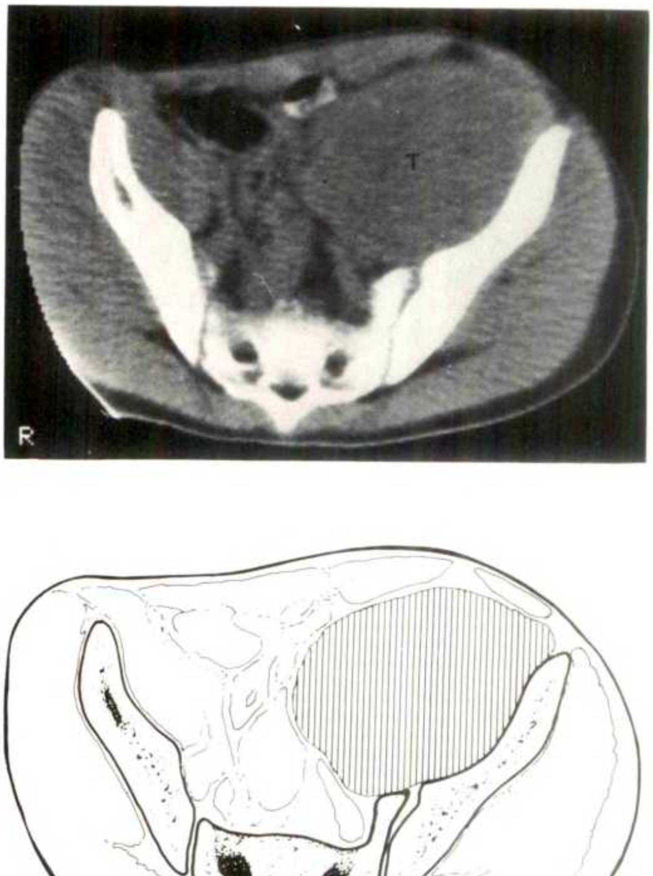

Figure 4 *Pelvic CT scan and diagrammatic representation showing a large rhabdomyosarcoma* (T) *arising in the left iliacus muscle and extending across the anterior aspect of the ipsilateral sacro-iliac joint (case 9)*

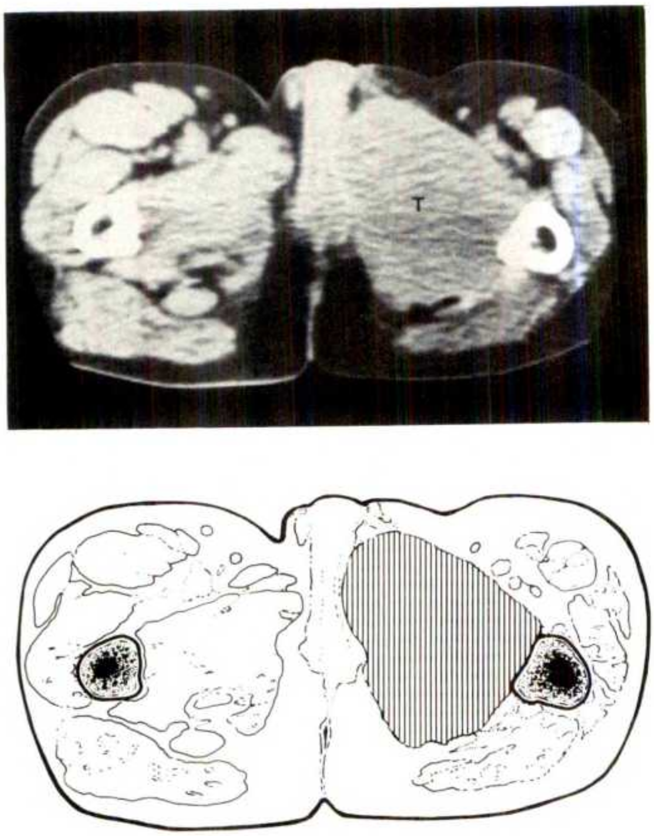

Figure 5 *CT scan of the proximal thighs and diagrammatic representation showing a synovial sarcoma* (T) *in the region of the left adductor musculature invading the root of the penis (case 10)*

their site. Tumours of the buttock or innominate bone that are well localized and do not extend through the greater sciatic notch are usually resectable either by *en bloc* radical resection or modified hindquarter amputation depending on the nature of the tumour and its histological grade[9]. Modified hindquarter amputation for buttock tumours involves covering the large posterior defect with an anterior myocutaneous flap based on the quadriceps femoris muscle and supplied by the superficial femoral artery[12,13]. This procedure is not possible if anterior tumour extension involves the common or external iliac vessels, a feature which can be easily demonstrated by CT.

Acknowledgements

We are grateful to Mr M. Duffy for preparing the diagrammatic representations of the CT scans.

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Evaluation of the prognostic factors in gastric cancer: the effect of chemotherapy on survival

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This is a retrospective review of 328 consecutive patients with histologically confirmed gastric adenocarcinoma diagnosed in one centre between 1974 and 1984. Of these patients, 128 (39 per cent) had a curative resection, 32 (9·8 per cent) had a palliative resection, 33 (10·0 per cent) had a gastro-enterostomy, 26 (7·9 per cent) had a Celestin tube inserted, 58 (17·7 per cent) had a laparotomy alone, and 51 (15·5 per cent) had no surgical procedure. The 5 year survival was 11 per cent but all long term survivors were patients who had a curative resection. Using multivariate analysis the best predictor of survival after curative resection was the presence or absence of serosal involvement ($P=0{\cdot}0004$)*. Patients with a long history of presenting symptoms* (>6 *months) survived longer than those with a short history* ($P=0{\cdot}001$)*. The impact of chemotherapy on the survival of 202 patients with advanced gastric cancer was analysed by multivariate analysis. The median survival of the 50 patients receiving combination chemotherapy was better than that of the 152 who did not (median survivals 160* versus *71 days;* $P<0{\cdot}001$)*. When deaths occurring within 14 days of diagnosis were excluded, the significance value dropped to* $P=0{\cdot}02$*. Comparison of the groups treated between 1974 and 1979, when 8 per cent of 92 patients received chemotherapy, with 1980–1984, when 45 per cent of 110 patients received chemotherapy, showed no significant difference in survival.*

Keywords: Gastric cancer, chemotherapy

The incidence of gastric cancer has declined in the United Kingdom during the past 10 years. Despite this fall it remains the third most common cause of cancer deaths in men and the fourth most common cause of cancer deaths in women[1]. Over 11 000 new cases are diagnosed each year in the UK. Although there have been a number of studies of the natural history of gastric cancer from the USA and Europe, many use data derived from the 1930s and 1940s[2–5] or use data compiled from several centres[6]. There are relatively few contemporary natural history studies[7] and we know of none from Scotland. The present study describes the natural history of gastric cancer in a group of patients diagnosed consecutively in one centre in Scotland.

Chemotherapy is now more widely used in the treatment of gastric cancer, a change stimulated by some of the early results obtained in the USA with combination chemotherapy regimens[8,9]. Although it is clear that patients who respond to chemotherapy live longer[10], there is little evidence that chemotherapy improves overall survival rates. This issue can only be addressed fully by a randomized prospective trial. Nevertheless, the present retrospective review allows investigation of the contribution of chemotherapy to overall survival. During the last 5 years of the study a Medical Oncology unit was established in the centre and a larger proportion of patients with advanced disease received chemotherapy. This allows comparison of the survival of patients with advanced disease during two periods, one when chemotherapy was rarely given and the other when chemotherapy was frequently given.

Patients and methods

We reviewed the clinical records of all patients with histologically proven gastric adenocarcinoma diagnosed in Glasgow Royal Infirmary between 1 January 1974 and 31 December 1984. We included patients with tumour of the cardia which had spread to involve the oesophagus. All patients were registered with the West of Scotland Cancer Surveillance Unit which records the data of diagnosis, date of death and the cause of death in all cancer patients from this region. The following data were abstracted: duration and type of symptoms, details of operative procedure, pathology of the resected specimen and details of any chemotherapy. The sites of recurrent disease were recorded. Local relapse was defined as tumour recurrence identified endoscopically or by barium studies or tumour recurrence within the gastric bed (identified at re-operation, post mortem, or by abdominal ultrasound or CT scan). Distant relapse was defined as tumour recurrence at all other sites including distant peritoneal spread and liver metastases.

Patients with advanced gastric cancer were defined as those in whom it was not possible to effect a surgical cure. Curative resections were defined as those in which there was no residual macroscopic disease after surgery.

No patient was given radiation therapy.

Statistical analysis

Data were analysed on the Glasgow University's Computer (ICL 2976). Survival was analysed by the life table method. Using Cox's Regression Model, the effects on survival of the following independent variables were examined: duration of symptoms before diagnosis, type of surgery, lymph node involvement, serosal involvement, resection margin involvement, site of primary tumour, presence of liver metastases, tumour histology and treatment with chemotherapy.

Results

During the 11 year period 330 patients were diagnosed as having histologically confirmed gastric cancer in Glasgow Royal Infirmary. Adequate clinical records and follow-up were available for 328 patients and the remaining 2 patients have therefore been excluded from analysis. The diagnosis was rare under the age of 45 years and the male to female ratio was 1·45:1 (*Table 1*). At presentation (*Table 2*) 30 per cent of patients had

Table 1 *Characteristics of 328 patients with gastric cancer*

Age (years)	Male (*n*)	Female (n)
<45	10	5
45–54	32	5
55–64	50	33
65–74	71	54
>75	31	37
Total	194	134

Table 2 *Presenting symptoms in 328 patients with gastric cancer*

Presenting symptoms	Number of patients
Anorexia and weight loss	272 (83)
Dysphagia and vomiting	210 (64)
Dyspepsia/abdominal pain	211 (64)
Unexplained anaemia	92 (28)
Emergency bleed/perforation	55 (17)

Values in parentheses are percentages

Table 3 *Survival of patients with gastric cancer according to operative procedure*

Primary treatment	No. of patients (%)	Percentage surviving at years 1	2	3	4	5	Median survival (months)
Curative resection	128 (39·0)	63	47	36	30	24	21
Palliative resection	32 (9·8)	27	14	3	3	0	6
Gastro-enterostomy	33 (10·1)	8	0	0	0	0	4
Celestin tube	26 (7·9)	8	4	4	4	0	2
Laparotomy alone	58 (17·7)	9	0	0	0	0	2
No surgery	51 (15·5)	12	6	3	3	3	1

an abdominal mass, 6 per cent were jaundiced and 3 per cent had lymphadenopathy.

Surgical procedures

All except 51 patients (15·5 per cent) had some form of surgical treatment. The types of operation and survival of patients for each subgroup are shown in *Table 3* and *Figure 1*. Almost all of the long term survivors came from the curative resection group, a group which survived significantly longer ($P<0{\cdot}01$) than any other. Patients who had a palliative gastro-enterostomy did not survive significantly longer than those having laparotomy alone, Celestin tube insertion or no surgery. The 11 years were arbitrarily divided into two periods, 1974–1979 and 1980–1984. There was no change in the proportion of patients undergoing each surgical procedure during the two periods. In particular, the number of patients having curative resection remained the same (*Table 4*). However, operative mortality (death within 30 days of surgery) for the curative resection group changed from 17·6 per cent between 1974 and 1979 to 8·4 per cent between 1980 and 1984. We have not analysed operative mortality for the other groups because it is often difficult to differentiate between deaths due to operation and those due to progression of disease.

Survival of curative resection group

Despite curative resection, only 24 per cent of these patients were alive five years after diagnosis (*Table 3*). To define the prognostic factors for this group, we examined the effects of site of primary tumour, serosal margin involvement, resection margin involvement and lymph node involvement (as determined by histological examination of the resected specimen) on survival. The results are shown in *Figure 2* and in *Table 5*. (In five patients the status of the serosa, and in two patients the status of the margins, were unknown.) All patients with resection margin involvement relapsed and died. Otherwise, serosal involvement was the best predictor of survival ($P=0{\cdot}0004$). Indeed, all but five patients with resection margin involvement had serosal involvement. Lymph node involvement was only a significant factor when the serosa and margins were not involved (*Table 6*). Survival related to the site of primary tumour is shown in *Table 7*. Survival was poorer ($P<0{\cdot}05$) for patients with tumours of the cardia compared with the body or antrum. This was mainly because resection margin involvement was more frequent with tumours of the cardia (39·5 per cent) than with tumours of the body (16·3 per cent) or antrum (21·4 per cent) ($P=0{\cdot}04$). The degree of differentiation of the cancer had no significant influence on survival (*Table 8*), although patients with well differentiated tumours had a better prognosis.

Endoscopy as a means of establishing the diagnosis had no effect on survival: the 102 patients undergoing endoscopy had a median survival of 663 days; the 26 patients who did not have endoscopy had a median survival of 570 days ($P=0{\cdot}22$). Analysis of the duration of presenting symptoms revealed that patients with a long history (> 6 months) survived longer than patients with a short history (< 6 months) (*Figure 3*). This finding persisted even when an adjustment was made, using Cox's regression model, for the prognostic factors described above ($P<0{\cdot}001$).

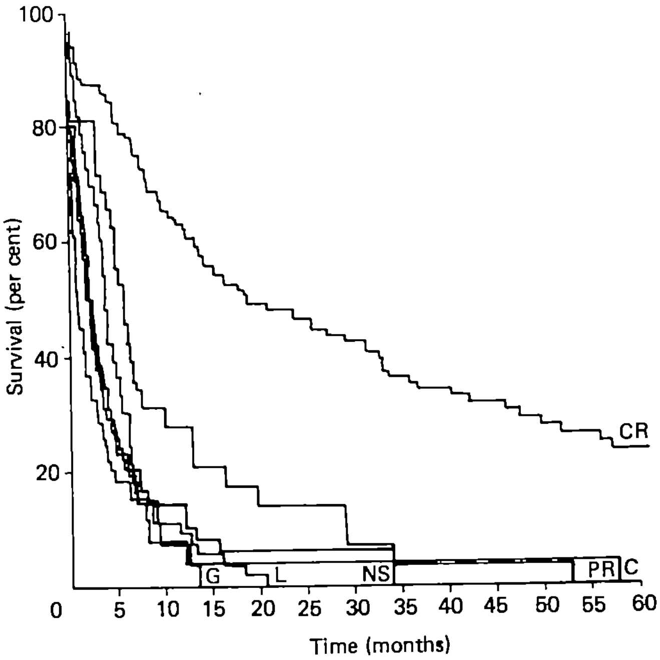

Figure 1 *Survival by surgical procedure in 328 patients with gastric cancer. (CR, curative resection:* n=*128; PR, palliative resection:* n=*32; G, gastro-enterostomy:* n=*33; C, Celestin tube:* n=*26; L, laparotomy:* n=*58; NS, no surgery:* n=*51.) Survival of CR* versus *PR:* $P<0{\cdot}001$. *Survival of PR* versus *G+L+NS:* $P<0{\cdot}01$

Table 4 *Operative procedure by period*

Operative procedure	1974–1979	1980–1984
Curative resection	39·2	38·6
Palliative resection	10·8	9·0
Gastro-enterostomy	8·5	11·6
Celestin tube	8·5	7·9
Laparotomy alone	22·3	14·8
No surgery	10·8	18·0

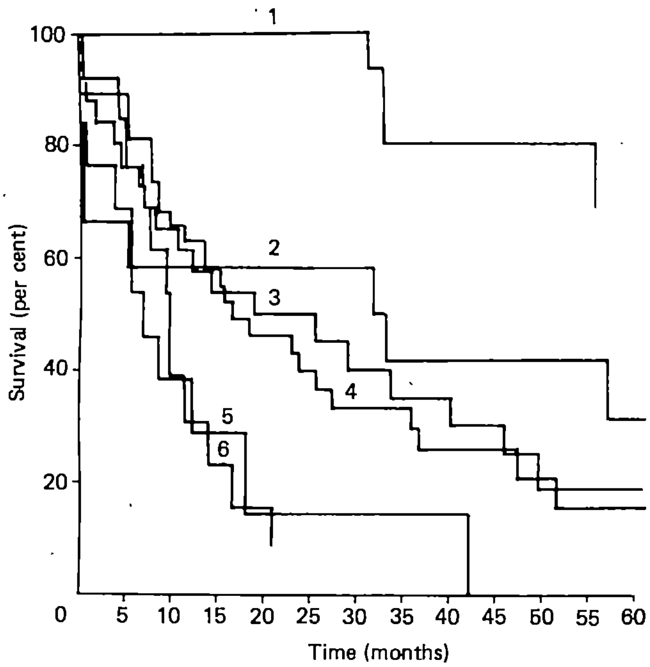

Figure 2 *Survival by serosal involvement (S), resection margin involvement (M) and lymph nodes involvement (N) in 128 patients having a curative resection for gastric cancer.*

	S	*M*	*N*	*Number*
1	–	–	–	*21*
2	–	–	+	*12*
3	+	–	–	*26*
4	+	–	+	*38*
5	+	+	–	*13*
6	+	+	+	*13*

1+2 versus *3+4*, P=*0·02*
3+4 versus *5+6*, P<*0·01*

Table 5 *Survival by serosal involvement, resection margin involvement and lymph node involvement in 128 patients undergoing curative resection for gastric cancer*

	No. of patients	Percentage surviving at years					*P*
		1	2	3	4	5	
Serosa							
Positive	90	54	35	26	18	13	0·0004
Negative	33	85	78	59	59	47	
Margins							
Positive	31	41	7	7	0	0	0·0005
Negative	95	69	58	43	36	28	
Nodes							
Positive	65	55	37	27	22	17	0·04
Negative	63	71	57	45	37	31	

Pattern of recurrence

Seventy-six per cent of all patients having a curative resection are dead. The sites of recurrent disease are shown in *Table 9*. Of the patients with resection margin involvement, 53·2 per cent developed local relapse alone or in combination with distant relapse.

The impact of chemotherapy on the survival of patients with advanced disease

Two hundred and two patients had advanced disease at presentation (this includes two patients who had curative resections subsequent to chemotherapy). Of these 202 patients, 50 were given chemotherapy. Forty-five received FAM (5-fluorouracil, Adriamycin and Mitomycin-C given as outlined in reference 10), three received TNO-6 (an analogue of cisplatin) and two received 5-fluorouracil only.

The effect of chemotherapy on survival was analysed using Cox's regression model. Patients who received chemotherapy survived significantly longer ($P<0{\cdot}001$) than those who did not (*Table 10*). To correct for patient selection for chemotherapy all deaths within 14 days of diagnosis were excluded. The significance value changed to $P=0{\cdot}02$ once these deaths had been excluded. In a further effort to elucidate the effect of chemotherapy on survival we compared the survival of patients with advanced disease from the period 1974–1979 (when 8 per cent of patients received chemotherapy) with the survival of patients from the period 1980–1984 (when 45 per cent of patients received chemotherapy). We found no significant difference ($P=0{\cdot}4$) in survival rates, suggesting that chemotherapy did not influence prognosis.

Discussion

The survival of this unselected series of patients was related to the type of surgical procedure performed. All long term survivors were derived from the group of patients in whom there was complete clearance of macroscopic disease at the time of resection. However, although 39 per cent of all patients had such a 'curative resection', only 11 per cent achieved long term

Table 6 *The effect of lymph node involvement on survival in 128 patients undergoing curative resection for gastric cancer*

Lymph node	Resection margin	Serosa	No.	Percentage survival	
				2 year	5 year
+ve	–ve	–ve	12	58	31
–ve	–ve	–ve	21	100	70
+ve	–ve	+ve	38	40	16
–ve	–ve	+ve	26	50	18
+ve	+ve	+ve	13	5	0
–ve	+ve	+ve	13	16	0
+ve	+ve	–ve	2	—	—
–ve	+ve	–ve	3	—	—

Table 7 *Survival by the site of the primary tumour in 125 patients undergoing curative resection for gastric cancer*

Site of primary tumour	No. of patients	Percentages surviving at years				
		1	2	3	4	5
Cardia	38	47	27	23	13	13
Body	43	68	54	45	35	28
Antrum	42	70	53	31	31	27

In three patients the site of primary tumour was not known

Table 8 *Survival by histology in 128 patients undergoing curative resection for gastric cancer*

Differentiation	No. of patients	Percentage surviving at years					Median survival (days)	*P*
		1	2	3	4	5		
Well	18	71	53	53	46	39	>1000	n.s.
Moderate	42	68	56	41	36	31	875	
Poor	68	59	41	28	20	15	544	

survival. Serosal involvement was the main determinant of survival. The group with serosal involvement had a 5 year survival rate of 13 per cent compared with 47 per cent for the group without. One explanation for the strong correlation between serosal involvement and survival, is that patients with serosal involvement have free cells in the peritoneal cavity, a contention supported by washing studies[11]. Therefore it is possible that these patients have micrometastasis at presentation.

Histological examination of the resected specimens showed that 24 per cent of our curative resection patients had tumour extending to the resection margin. The British Stomach Cancer Group reported a 22 per cent incidence of resection margin involvement in their series of 390 patients[12], and Papachristou *et al.*[13] found that, following subtotal or total gastrectomy, 20 per cent of their 350 patients had tumour involving the resection margin. This problem may be overcome if the resection margins are examined by frozen section at the time of operation[13]. The prognosis for patients with resection margin involvement is known to be extremely poor[12], and none of our 31 patients in this category survived for more than 3 years. However, of our 31 patients, 84 per cent also had serosal involvement which implies that their survival would have been limited, regardless of resection margin involvement. In Papachristou's study only 23 per cent of the 73 patients with resection margin involvement developed anastomotic recurrence. The majority of patients died of metastatic disease before such recurrence became manifest[13]. It is possible that resection margin involvement, like serosal involvement, is a marker of aggressive, metastatic stomach cancer. Lymph node involvement is also regarded as a major survival determinant in gastric cancer[14]. Our experience suggests that this is not the case and that spread of tumour to the lymph nodes only has prognostic significance in patients without serosal involvement.

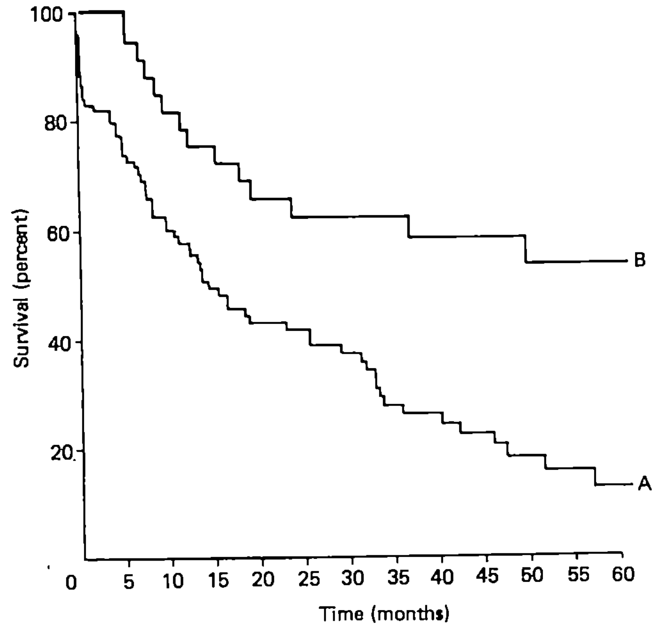

Figure 3 *Survival by duration of symptoms in 121 patients having a curative resection for gastric cancer. A, <6 months* ($n=88$)*; B, >6 months* ($n=33$)*.* $P<0.001$

In the curative resection group, patients with a long history of presenting symptoms had a better prognosis than those with a short history. This factor remained significant even when the data was subjected to multi-variant analysis. This observation was first made in 1952 by Swynnerton and Truelove[2] and appears to apply to patients with early gastric cancer as well[15]. It is probable that the subgroup of tumours associated with a long history behave less aggressively and are therefore more amenable to successful surgical intervention. A recent study from Japan[16] has shown that long term survivors after gastrectomy for gastric cancer have a high frequency of the HLA-DR4 antigen when compared to normal healthy controls and other gastric cancer patients. Thus, it will be important to examine the HLA antigens of patients with a long duration of presenting symptoms.

There is still debate about the best surgical approach to gastric cancer[17]. In particular, it remains controversial whether subtotal gastrectomy is as effective as total gastrectomy in effecting a cure[18,19]. Pivotal to the argument is the consistently higher operative mortality of total gastrectomy (11·5–37·2 per cent) compared with that of subtotal gastrectomy (3.2–23·7 per cent)[18]. Therefore, although total gastrectomy should theoretically provide more long term survivors, this advantage is offset by the greater number of early operative deaths, especially in the older patients. Randomized studies are required to resolve this controversy but, from our experience, length of history of presenting symptoms should be part of the stratification of such studies. It would also be advisable to incorporate assessment of the cytology of peritoneal aspirates since this clearly has a major influence on survival[11].

The pattern of failure after resection for gastric cancer has been the subject of a number of reports[19–22]. In two post-mortem studies locoregional recurrence was found in 80 per cent[19] and 96 per cent[20] of patients following subtotal gastrectomy. However at post mortem almost 75–90 per cent of patients also have distant metastases, these most commonly involving other abdominal organs[22]. Our own data suggest that at least two-thirds of patients have distant metastases at the time of relapse. Local recurrence alone was found in only 33 per cent of patients but this is probably an overestimate, since it is likely that some of these patients have undetected metastatic disease.

Table 10 *Effect of chemotherapy on the survival of patients with advanced disease*

	All patients		Excluding deaths within 14 days	
	Median survival (days)	Percentage surviving 1 year	Median survival (days)	Percentage surviving 1 year
No chemotherapy ($n=152$)	71	9	108	12
Chemotherapy ($n=50$)	160	24	155	23

All patients: chemotherapy *versus* no chemotherapy, $P<0.001$
Excluding early deaths: chemotherapy *versus* no chemotherapy, $P=0.02$

Table 9 *Pattern of recurrence after curative resection for gastric cancer*

Findings at the time of resection		No. of patients	Site of relapse (per cent)				
Serosa	Margins		None	Local	Distant	Both	Not known
+ve	−ve	64	23·4	14·1	12·5	18·7	31·2
+ve	+ve	26	11·5	23·1	7·7	30·1	26·9

Patients with no serosal involvement have been excluded

Several classifications are used to describe the histology of gastric cancer[23–25]. Most pathologists report the degree of differentiation of the tumour but others divide gastric adenocarcinoma into intestinal and diffuse types as described by Lauren *et al.*[25] It has been suggested that the intestinal type is more common in areas with a high incidence of gastric cancer[26] and that it carries a better prognosis than the diffuse type[27]. However, this is controversial and a recent study from the UK failed to reveal any difference in the incidence of intestinal and diffuse types between areas with a low and high prevalence of gastric cancer[28]. Also, there appears to be some overlap in the different classifications. Kubo has reported that well differentiated tumours tend to be intestinal and poorly differentiated tumours diffuse[29]. Moreover, there undoubtedly are problems classifying gastric cancer according to the Lauren classification[25]. Caygill *et al.*[30] found that 30 per cent of the tumours were unclassifiable or had a mixture of intestinal and diffuse forms. Therefore we have reported histology simply in terms of degree of differentiation. The degree of differentiation did not significantly affect the survival of patients having a curative resection. However, there was a clear trend in favour of a better prognosis for patients with well differentiated tumours.

We have not described the incidence of early gastric cancer in our patients (which is defined as tumour which has not penetrated the submucosa). By inference it is likely that the incidence was low because the overall prognosis of our surgically resected group was so poor. Early gastric cancer in the UK is now thought to be identical to the Japanese variety[31] and the notion that Japanese stomach cancer is biologically different to Western stomach cancer is untenable. It seems likely that the higher proportion of early gastric cancer in Japan is due to more aggressive diagnostic and screening policies. Indeed, Houghton *et al.*[32] found that early gastric cancer now comprises 12 per cent of all gastric cancers and attributed this increased incidence to the more routine use of endoscopy. However, in our series, endoscopy as a means of diagnosis had no impact on survival. One possible explanation is that to obtain maximum benefit from endoscopy this procedure must be linked to a more comprehensive programme for early detection[33]. This would include the selection of high risk groups for endoscopy, such as patients over 40 years presenting for the first time with dyspepsia or those patients who have had surgery in the past for peptic ulcer disease[34].

As a palliative procedure, resection of the gastric primary, even in the presence of solitary or multiple liver metastases, improves survival[35–37], and more importantly may overcome some of the distressing symptoms which can develop. In our experience, palliative resection was associated with a longer survival (6 months) when compared with the survival of patients in the other advanced disease groups (1–4 months). However, patients who had a palliative bypass survived no longer than those who had a laparotomy alone or no surgical procedure. This of course does not necessarily mean that palliative bypass does not contribute to 'quality of life' since measuring duration of survival ignores this factor, but it should mean that 'bypass' is not axiomatic for patients with irresectable tumour.

When cytotoxic drugs such as 5-fluorouracil, Adriamycin, cisplatin or Mitomycin-C are given as single agents in the treatment of gastric cancer, approximately 15–25 per cent of tumours regress partially. The regression usually lasts for only 3–5 months and is of little biological significance or benefit to the patient[38]. Following the introduction of combination chemotherapy regimens, especially FAM, response rates in the region of 35–40 per cent were reported[9,10]. Of more importance was the observation that these responses lasted longer (10 months) and that responding patients survived for a median of 17 months. Untreated, advanced gastric cancer has a very poor prognosis: a median survival of 4 months was reported in one North American series[39]. Therefore it was considered possible that combination chemotherapy was prolonging survival. As a result, there have been few randomized trials comparing the survival of patients treated with chemotherapy as FAM, against no chemotherapy.

The present natural history study provides an opportunity to investigate the effects of chemotherapy on the overall survival of patients with advanced disease. In the second period of the study, 45 per cent of patients received chemotherapy compared with 8 per cent of patients who received chemotherapy during the first period. In other respects the two patient populations were very similar. In particular, there was no major change in the type or proportions of surgical procedure performed; both groups were matched for the presence of liver metastases, the patients were drawn from a consecutive series thus eliminating the bias normally created by patient selection for a retrospective study, and information was available on virtually all patients for follow-up. Using multivariate analysis, patients with advanced disease who received chemotherapy lived significantly longer than those who did not. However, when all deaths within 14 days of diagnosis were excluded from analysis, the difference was less marked, although still significant ($P = 0{\cdot}02$). The rationale for excluding early deaths was based on the assumption that patients selected for chemotherapy are usually more fit than those who are not, and that such patients are normally expected to live more than 14 days. The next step in the analysis was to compare the survival of patients with advanced disease during the two periods, one when chemotherapy was rarely given and the other when almost half of the patients were given chemotherapy. The survival of these two groups of patients was identical.

Why should a treatment which can produce tumour regression in 35–40 per cent of patients produce such dismal results? Chemotherapy is not devoid of side effects and may well contribute to an increased morbidity and mortality in patients who do not respond. Certainly, this is true of more toxic regimens[40], and this effect may outweigh the beneficial effects of chemotherapy in some patients. Thus, in order to optimize the use of chemotherapy, there must be careful pre-treatment selection of patients, such as those patients with tumours giving rise to symptoms or tumours occurring in young patients. The administration of chemotherapy must also be closely monitored so that toxicity is minimized, particularly that related to the gastrointestinal tract which may be achieved by a number of anti-emetics[41,42].

The prognosis for patients with gastric cancer remains very poor. Surgical intervention offers the only prospect of cure and is only likely to be successful in patients whose tumours have not penetrated the serosa. On the basis of current evidence, there is no place for the routine use of combination chemotherapy regimens for the treatment of advanced gastric cancer—such treatment should only be given within the context of a clinical trials or for certain defined clinical situations.

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Relative contribution of bile and pancreatic juice duodenogastric reflux in gastric ulcer disease and cholelithiasis

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Bile acid concentrations, phospholipase A_2 activity and pH in the stomach were measured in the fasting state and for 2 h after a fat-containing test meal in patients with an active gastric ulcer (GU), in patients with gallstones before and after cholecystectomy and in normal subjects. Fasting and peak postprandial bile acid concentrations in the stomach were low in all normal controls. Although high concentrations were found in many patients with GU ($P<0.01$), similar concentrations were found in many patients with radiologically non-functioning gallbladders containing gallstones (NFG) ($P<0.01$) and also after cholecystectomy (AC) ($P<0.01$). Fasting intragastric phospholipase A_2 activities were similar, and very high in GU and NFG patients compared with control subjects ($P<0.01$). High values were not found after cholecystectomy. There was no difference in pH profile or in postprandial phospholipase A_2 between patient groups. Since patients with cholelithiasis or after cholecystectomy are not known to have an increased incidence of gastric ulceration, the significance of duodenogastric reflux in the aetiology of gastric ulcers must be questioned. If reflux does produce ulcers in GU patients then factors in addition to bile acid are probably involved. However, neither patterns of phospholipase A_2 reflux nor pH profiles can explain the absence of gastric ulceration in those patients with gallstones who reflux large quantities of bile acid.

Keywords: Duodenogastric reflux, phospholipase A_2, bile acids, gastric ulcer, gallstones

Damage to the gastric mucosa by refluxed bile acid and lysolecithin has been proposed as an important cause of gastric ulcer disease[1–3]. Both bile acid[4–11] and lysolecithin[12,13] can cause gastric ulcers in experimental animals and higher intragastric concentrations of both agents have been reported in gastric ulcer patients than in controls[1–3,14,15]. Many, though not all, studies have shown increased reflux of marker substances from the duodenum to the stomach in gastric ulcer patients when compared with controls[16–21], though increased reflux has also been reported in cholelithiasis[22,23]. Thus, in Capper's original radiological studies, reflux of barium from duodenum to stomach was absent in control subjects but was noted in all 17 gastric ulcer patients and in 16 out of 18 patients with gallstones[22]. Intragastric concentrations of bile acids and lysolecithin in patients with gallstones have not previously been studied. If they are similar to those in gastric ulcer patients, the role of bile acid and lysolecithin in the aetiology of gastric ulcer disease will need to be re-evaluated as there is no evidence that patients with gallstones are more likely to develop gastric ulcers.

We have studied both fasting and postprandial intragastric concentrations of total bile acid and phospholipase A_2 in patients with gastric ulcers, in patients with gallstones and in controls. Phospholipase A_2 is the pancreatic enzyme which converts biliary lecithin to lysolecithin. It is not consumed during this process and thus serves as a good marker of pancreatic reflux. Unlike lysolecithin, phospholipase A_2 remains stable in an acid medium and can be reliably assayed in the stomach[24].

Patients and methods

Patients

Five groups were studied:

1. Patients with an active type I gastric ulcer demonstrated at endoscopy and biopsy who were receiving no treatment (GU) ($n=11$).
2. Patients with gallstones in a radiologically functioning gallbladder on oral cholecystography (FG) ($n=6$).
3. Patients with gallstones in a radiologically non-functioning gallbladder (NFG) ($n=11$).
4. Patients after cholecystectomy (AC) ($n=8$).
5. A control group with no gastrointestinal symptoms or disease ($n=6$).

The presence of gallstones in the gallbladder in groups 3 and 4 was established by both ultrasonography and oral cholecystography and was subsequently confirmed at cholecystectomy. Patients with a functioning gallbladder had a well defined gallbladder on X-ray after an oral dose of sodium iopodate (6 g×2). Patients with a non-functioning gallbladder had no gallbladder opacification at oral cholecystography. Group 4 (AC) comprised those patients from groups 2 and 3 who consented to be restudied after their cholecystectomy. Patient details are shown in *Table 1*. Subjects in the control group volunteered for the study while they were in hospital for minor surgery for varicose veins or cutaneous lesions.

All patients were interviewed and a careful clinical history taken. Symptoms specifically sought included burning discomfort in the abdomen, burning discomfort in the chest, bitter reflux into the mouth, nausea, vomiting, belching, inability to finish meals and postprandial abdominal distension. Using a previously published scoring technique[25] the frequency and severity of each symptom was assessed on a three point numerical score and the score was combined to provide a value for the extent of dyspeptic symptoms (dyspeptic score: range

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0–36). This allowed comparison between reflux of bile acid and phospholipase A_2 and the presence of dyspeptic symptoms. Some of the patients with gallstones including all those with dyspepsia (score > 10) underwent alimentary endoscopy.

Test meal and sampling technique

After an overnight fast, a double-lumen orogastric tube (outside diameter 6 mm) was positioned in the dependent part of the stomach and its position confirmed using the water recovery test[26]. The patient was positioned semirecumbent and rested for 20 min before gastric contents were aspirated and discarded. Fasting gastric contents underwent continuous low pressure aspiration (−5 mmHg) for half an hour and a 20 ml sample of this collection was retained for analysis. Aspiration was discontinued and 300 ml of 10 per cent Intralipid was administered via the orogastric tube as a test meal. Gastric contents were mixed by repeated aspiration and re-introduction using a 60 ml syringe, before a 20 ml sample was withdrawn for analysis. Further 20 ml samples were taken at 30 min intervals for 2 h. Sampling was always preceded by mixing of gastric contents with the 60 ml syringe and the orogastric tube was left spigoted between samplings. All samples were stored at −70°C for subsequent analysis. Intralipid is an aqueous emulsion of soya bean oil (100 g/l), egg lecithin (6 g/l) and glycerol (12·5 g/l) with an osmolality of 280 mosml/l.

Table 1 *Patient details*

	Number (sex ratio)	Median age (years)	Age range (years)
Gastric ulcer	9M:2F	58	39–77
Gallstones, functioning gallbladder	0M:6F	56	24–76
Gallstones, non-functioning gallbladder	5M:6F	62	46–77
After cholecystectomy	2M:6F	66	58–70
Controls	4M:2F	58	46–56

Chemical analysis

Total bile acid concentration was measured by the steroid dehydrogenase technique as described by Murphy[27]. This enzymatic method, using 3α-hydroxysteroid dehydrogenase, measures the reduction of nicotinamide adenine dinucleotide ($NAD \rightleftharpoons NADH$) fluoroscopically. All 3 α-hydroxysteroids, both free and conjugated, are converted to the corresponding ketosteroid with formation of NADH.

Phospholipase A_2 was measured using a technique developed in our department and published in detail elsewhere[24]. Phospholipase A_2 activity was established using gas–liquid chromatography to measure the amount of palmitic acid released by the reaction.

The pH of the gastric sample was measured on an automatic pH meter (Autoburette AbU 13, Radiometer, Copenhagen).

Statistical methods

Results were expressed as fasting and peak postprandial concentrations for the process of statistical analysis. The distribution of the data is very skewed, therefore results were analysed using Kimber's test for many outliers of an exponential sample[28] in order to assess the incidence of very high values in the various groups. If all very high values belong to one group the test will be significant.

Results

Bile acid, phospholipase A_2 and pH results in the five patient groups are summarized in *Tables 2* and *3*. Individual bile acid results in NFG, AC and GU patients are displayed in *Figures 1* and *2* and the phospholipase A_2 results in *Figures 3* and *4*.

Fasting

Fasting bile acid concentrations were low in all controls (range 10–33 μmol/l) and FG patients (10–61 μmol/l) but markedly elevated bile acid concentrations were found in some NFG (10–3100 μmol/l), AC (10–1230 μmol/l) (*Figure 1*) and GU patients (10–1270 μmol/l) (*Figure 2*). The distribution of fasting bile acid levels in the NFG and AC patients did not differ significantly from that in the GU patients but results in each of these groups (NFG, AC, GU) differed significantly from results in the control group ($P<0·01$).

Table 2 *Fasting bile acid, phospholipase A_2 and pH results*

Group	Bile acid concentration (μmol/l)	Significance of difference from		Phospholipase A_2 activity (unit/l)	Significance of difference from		pH*
		Control	Gastric ulcer		Control	Gastric ulcer	
Gastric ulcer ($n=11$)	195 (10–1270)	$P<0·01$		410 (90–9290)	$P<0·01$		4·2 (1·5–7·6)
Functioning gallbladder on oral cholecystogram ($n=6$)	20 (10–61)	n.s.	$P<0·01$	14 (0–93)	n.s.	$P<0·01$	4·2 (1·8–7·6)
Non-functioning gallbladder ($n=11$)	92 (10–3100)	$P<0·01$	n.s.	72 (0–3000)	$P<0·01$	n.s.	4·8 (1·8–8·4)
After cholecystectomy ($n=8$)	28 (10–1230)	$P<0·01$	n.s.	19 (0–330)	n.s.	$P<0·01$	2·8 (1·7–6·7)
Controls ($n=6$)	23 (10–33)		$P<0·01$	17 (0–41)		$P<0·01$	5·8 (3·7–7·5)

Median concentrations shown with range of values in parentheses; *, no significant differences were found between groups for pH using Kimber's test

Table 3 *Peak postprandial bile acid, phospholipase A_2 and pH results*

Group	Bile acid concentration (μmol/l)	Significance of difference from		Phospholipase A_2 activity* (unit/l)	pH*
		Control	Gastric ulcer		
Gastric ulcer ($n=11$)	305 (33–4375)	$P<0·01$		91 (52–1640)	2·6 (1·7–6·8)
Functioning gallbladder on oral cholecystogram ($n=6$)	460 (16–1300)	n.s.	n.s.	124 (39–323)	2·7 (1·7–5·5)
Non-functioning gallbladder ($n=11$)	130 (29–2000)	$P<0·01$	n.s.	124 (10–880)	2·3 (1·7–6·1)
After cholecystectomy ($n=8$)	320 (86–1800)	$P<0·01$	n.s.	240 (43–454)	2·7 (1·8–7·2)
Controls ($n=6$)	48 (23–74)		$P<0·01$	156 (9–464)	4·6 (2·3–5·9)

Median concentrations shown with ranges in parentheses; *, no significant differences were found between groups for pH and phospholipase A_2 activity using Kimber's test

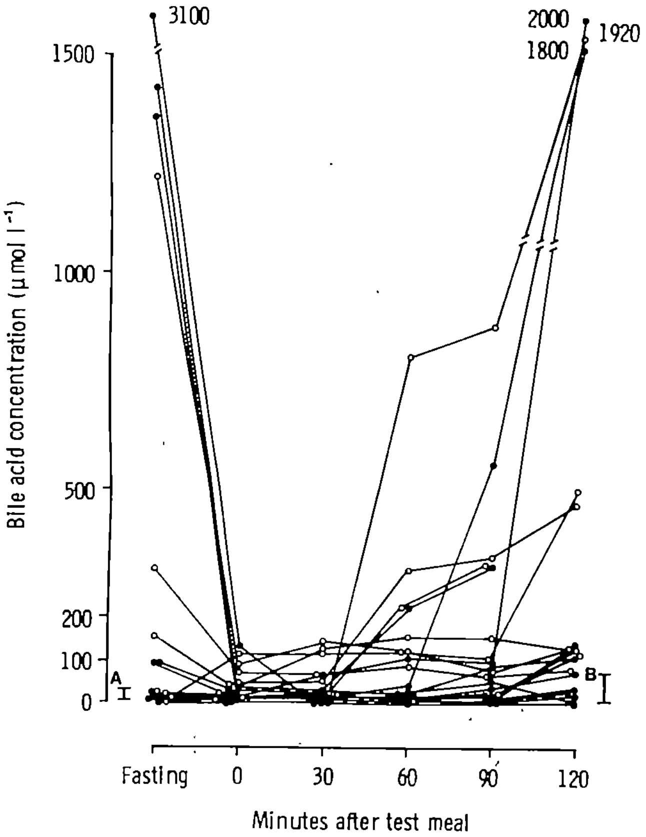

Figure 1 *Individual bile acid concentrations in the fasting state and after an Intralipid test meal.* ●, *non-functioning gallbladder patients;* ○, *patients after cholecystectomy;* I, *range of values in control subjects for A, fasting and B, peak postprandial concentrations*

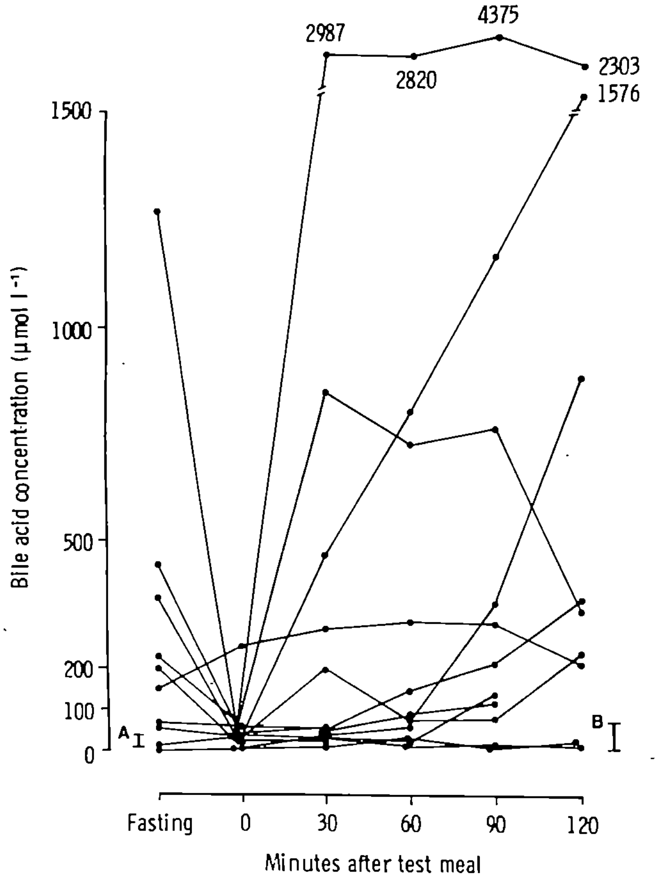

Figure 2 *Individual bile acid concentrations in the fasting state and after an Intralipid test meal in patients with an active gastric ulcer;* I, *range of values in control subjects for A, fasting and B, peak postprandial concentrations*

The pattern of fasting phospholipase A_2 results was similar to the fasting bile acid results in the controls, FG, NFG and GU patients (*Figures 3* and *4*). Patients with high fasting bile acid concentrations usually had elevated fasting phospholipase A_2 activity. There were low phospholipase A_2 activities in all controls (range 0–41 unit/l) and FG patients (0–93 unit/l) but markedly elevated activities in some NFG (0–3000 unit/l) and

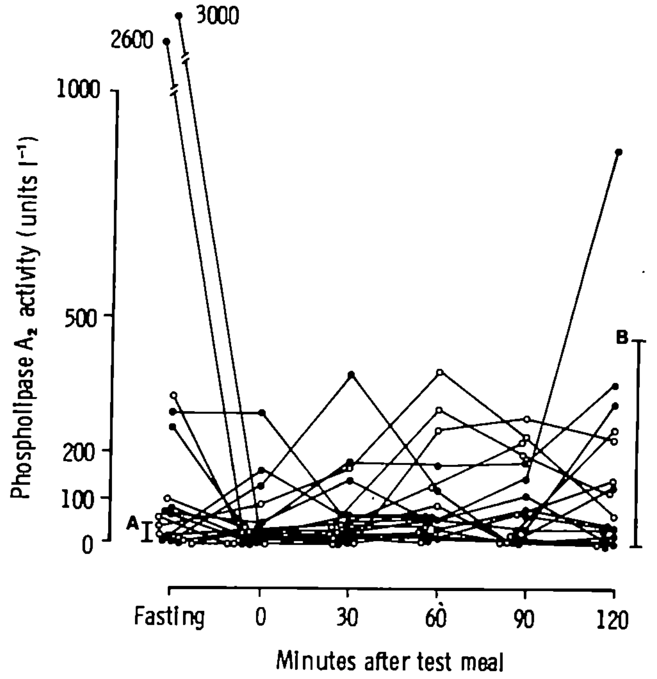

Figure 3 *Individual phospholipase A_2 concentrations in the fasting state and after an Intralipid test meal.* ●, *non-functioning gallbladder patients;* ○, *patients after cholecystectomy;* I, *range of values in control subjects for A, fasting and B, peak postprandial concentrations*

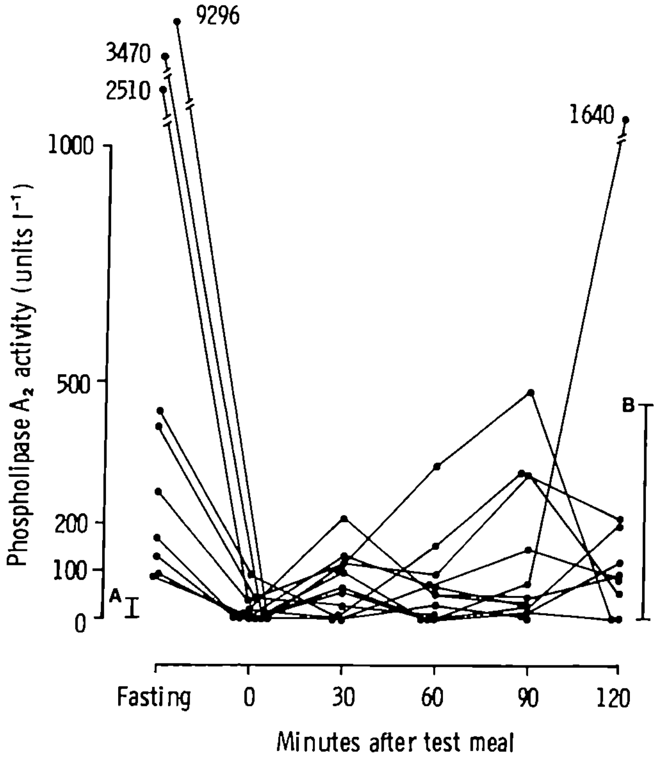

Figure 4 *Individual phospholipase A_2 concentrations in the fasting state and after an Intralipid test meal in patients with an active gastric ulcer.* I, *range of values in control subjects for A, fasting and B, peak postprandial concentrations*

GU patients (90–9290 unit/l); levels in NFG and GU patients were similar and those in both groups differed from the control results ($P<0.01$). The range of activities after cholecystectomy (0–330 unit/l) was much smaller than in the GU group, with no extremely high values occurring ($P<0.01$).

Postprandial

Peak postprandial bile acid concentrations were low in all controls (range 23–74 μmol/l) but elevated peak postprandial concentrations were seen in some patients in all other groups (FG, NFG, AC, GU). The distribution of results in the NFG, AC and GU groups were similar but results in each of these groups differed significantly from control values ($P<0.01$). Peak postprandial phospholipase A_2 activities in the control group (range 0–464 unit/l) showed greater variation than did the fasting values (0–41 unit/l). Consequently, the majority of peak postprandial phospholipase A_2 values in NFG, AC and GU patients fell within the range of activities found in control subjects and no significant differences were found between patient groups. However, very high peak postprandial phospholipase A_2 activities were only found in some NFG and GU patients.

The pH results in the groups did not differ significantly in the fasting or postprandial states. There was no evident relationship between pH and intragastric bile acid concentration or phospholipase A_2 activity.

Symptoms and reflux

In patients with gallstones there was no relationship between bile acid or pancreatic reflux and dyspeptic symptoms whether assessed as individual symptoms or as the total dyspeptic score. Thus, all patients with fasting or postprandial bile acid concentrations above 1000 μmol/l had negligible dyspeptic symptoms with total dyspepsia scores below 5 (out of 36) whereas all 5 patients with high dyspepsia scores (> 10) had bile acid concentrations of <121 μmol/l and phospholipase A_2 concentrations of <310 unit/l. There was no relationship between macroscopic gastritis and reflux of bile acid or phospholipase A_2 in patients who underwent endoscopy.

Discussion

One objection to the method we have employed is that the orogastric tube might disturb normal physiology and predispose to duodenogastric reflux. The results in our control group suggest that the orogastric tube does not induce reflux of bile acid or phospholipase A_2 and the stimulus of the tube is the same in all groups. A second objection to our methods is the use of an Intralipid test meal which is not an ideal physiological stimulus, being a mixture of solubilized fats without accompanying proteins and carbohydrates. In a pilot study we employed the more balanced Lundh meal as used by Dewar[15] but we found that it became particulate in the acid gastric medium making sampling very difficult and bile acid analysis in the liquid phase dubious. The similarity of bile acid concentrations in our control and gastric ulcer patients, compared with those obtained by others using more balanced meals[1,2,14,15,29,30] has reassured us that Intralipid is a satisfactory test meal.

Our control group is small but much larger numbers of controls have been studied previously[1,2,14,15,22,29,30]. Bile acid concentrations in the stomach were uniformly low in all these controls. Previous studies, with one exception, have corroborated our finding of significantly greater bile acid concentrations in gastric ulcer patients than controls[1,2,14,15]. The discordant study reported by Poxon *et al.*[31], found no difference in total bile acid concentrations, measured at hourly intervals over a 24 h period, between six GU patients and eight controls. They found that bile acid concentrations were below 520 μmol/l in all six GU patients, a range which is much smaller than that observed in other larger studies where values in excess of 3000 μmol/l have been observed. A further discordant report is that of Muller Lissner *et al.*[21] who, using a complicated isotopic technique, failed to demonstrate a greater rate of postprandial duodenogastric reflux of HIDA (^{99m}Tc-Sn-2,6-diethylacetanilidoiminodiacetate) in patients with gastric ulceration than in controls. Although high rates of reflux were observed in some patients with gastric ulcer, similar reflux rates were recorded in two out of ten controls. However, no information is given in this report about the selection of controls and their freedom from gastrointestinal symptoms. Furthermore, the technique gives no insight into bile acid concentrations in the stomach. The larger number of subjects in previously mentioned studies suggest that bile acid concentrations in controls are uniformly low and different from those in gastric ulcer patients. However, not all GU patients have elevated concentrations of bile acids in their stomach and some have levels well within the control range both in the fasting and postprandial states.

The principal aim of the present study was to compare bile acid and phospholipase A_2 concentrations in gastric ulcer patients with those seen in cholelithiasis. The validity of our findings is not compromised by the small size of the control group. Intragastric bile acid concentrations in many patients with gallstones in a non-functioning gallbladder and after cholecystectomy are as high as those seen in gastric ulcer disease, both in the fasting and postprandial states. Although delayed gastric emptying, which is a feature of gastric ulcer disease[32], could prolong the contact time between bile acids and the gastric mucosa, intragastric bile acid concentrations 2 h after the test meal were comparable in GU, NFG and AC patients. We have previously noted that patients with gallstones in a radiologically non-functioning gallbladder are more prone to postprandial duodenogastric reflux of HIDA than those with a functioning gallbladder[25]. This study has demonstrated that high bile acid concentrations in the fasting stomach are more common in those with a non-functioning than a functioning gallbladder but the relationship was not demonstrated in the postprandial state.

We have used phospholipase A_2 activity in the stomach as an indicator of pancreatic reflux. If bile is present in the stomach when pancreatic reflux occurs, the association of pancreatic phospholipase A_2 with biliary lecithin would result in the formation of lysolecithin (which is injurious to gastric mucosa in experimental studies). Our finding of greater fasting intragastric phospholipase A_2 activity in gastric ulcer patients than in controls accords with our previous finding of significantly elevated lysolecithin concentrations in overnight gastric samples from patients with gastric ulcer[3]. Phospholipase A_2 activities in NFG patients were similar to those in GU patients and significantly greater than in controls. Since those GU and NFG patients who had elevated fasting bile acid concentrations usually had elevated phospholipase A_2 activity, it is probable that their intragastric lysolecithin concentrations were also similar.

Fasting phospholipase A_2 activities after cholecystectomy were lower than those in gastric ulcer patients. This might protect patients after cholecystectomy from developing gastric ulceration but would not explain the absence of ulceration in NFG patients, especially as very high postprandial phospholipase A_2 activities were seen in NFG and GU patients.

A higher intragastric pH in patients with NFG and AC than in GU patients could explain the absence of gastric ulceration in cholelithiasis as bile acid damage to gastric mucosa can be potentiated in an acid medium[33]. However, in the present study pH profiles in the two diseases were similar. Although reduced gastric acid secretion has been reported in patients with gallstones[22], low gastric acid secretion is also a feature of gastric ulcer disease.

Ritchie and others have shown that individual bile acids differ in their capacity to damage gastric mucosa[34–36]. Harman has also shown that the relative barrier breaking potential of individual bile acids depends on the total concentration of bile acids in the mixture[37]. Thus, the composition of the individual bile acids refluxed into the stomach may differ in patients with gallstones in a non-functioning gallbladder from that in gastric ulcer patients. The profile of individual bile acids in the duodenum is certainly altered by cholecystectomy[38] and loss of gallbladder function due to gallstones would produce similar effects. However, the increased chenodeoxycholate composition seen after cholecystectomy[38] might well render the bile mixture more, rather than less, noxious to gastric mucosa[37]. We are at present investigating profiles of individual bile acids in the stomach of patients with gastric ulcer and gallbladder disease.

We have hypothesised previously that reflux of bile acids into the stomach in patients with gallstones could be associated with dyspeptic symptoms and gastritis[23]. Gallstone patients would then share many of the features of gastric ulcer patients but would presumably lack some additional factor which leads to mucosal breakdown in gastric ulcer disease. In this study, however, we found no association between reflux of bile acids or phospholipase A_2 and dyspeptic symptoms. Patients with marked fasting and postprandial reflux frequently had no evidence of macroscopic gastritis at upper alimentary endoscopy. The evidence from this study suggests that reflux in gallstone patients is not associated with deleterious effects upon their symptoms, or the gastric mucosa.

There are several other factors that need to be studied to understand the possible significance of our findings. It may be that there are differences of gastric emptying between gallstone and GU patients, mucosal damage may occur during the night rather than during the day, and it is not clear whether a high bile acid concentration for a short time is more or less damaging than moderate bile acid concentration over a long period.

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Gastrointestinal haemorrhage from a second source in patients with colonic angiodysplasia

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Angiodysplasia of the colon is increasingly recognized as a cause of obscure gastrointestinal haemorrhage. On review of 71 patients with angiodysplasia, 40 came to surgery. Of these, nine (22·5 per cent) were also found to have small bowel lesions, either at the original laparotomy (7) or later when further investigations were performed for recurrent bleeding. Angiodysplasia can only be confidently diagnosed as the source of blood loss if seen to be actively bleeding. If a synchronous small bowel lesion is seen, we recommend that it should be removed at the same time as the colectomy.

Keywords: Gastrointestinal haemorrhage, angiodysplasia, synchronous lesions

Gastrointestinal tract bleeding accounts for some 30 000 admissions to hospital each year in Britain[1]. About 5 per cent of gastrointestinal bleeding is from obscure causes and sites[2]. Obscure bleeding can be defined as that where the cause or site is not detected by routine diagnostic methods, including panendoscopy, upper and lower gastrointestinal tract barium series, isotope scans and, occasionally, even laparotomy. Colonic angiodysplasia is frequently diagnosed by angiography or colonoscopy in these cases[3].

However, re-bleeding rates following treatment of colonic angiodysplasia have been reported to be as high as 19 per cent[4]. We have noticed that patients with colonic angiodysplasia often have a second lesion which may result in gastrointestinal bleeding. The aim of this paper is to describe these other lesions found in association with angiodysplasia and to discuss their management.

Patients and methods

Seventy-one patients with gastrointestinal bleeding and right sided colonic angiodysplasia demonstrated by colonscopy or angiography presented between 1978 and 1985. Their outcome is shown in the flow chart. Thirty-one stopped bleeding and needed no further treatment. Forty patients continued to bleed and underwent laparotomy. A thorough laparotomy revealed no other lesion in 31 patients and a right hemicolectomy was performed. Three patients died in the postoperative period. Of the remaining 28, seven (25 per cent) rebled. Follow-up has been from 4 months to 5 years, two patients requiring further surgery within 3 months and two after 3 years. The rebleeding was due to gastric angiodysplasia (1), von Willibrand's disease (1), jejunal arteriovenous (A–V) malformation (1) and chronic pancreatitis (1). In three patients no cause for the rebleeding was found. The surgery required to treat rebleeding included a jejunal resection, a partial gastrectomy and a distal pancreatectomy.

Nine patients were noted to have small bowel lesions at laparotomy. Seven had the small bowel lesions alone excised and no right hemicolectomy. The lesions excised were: Meckel's diverticulum (4), ileal carcinoid (1), multiple jejunal A–V malformation (1) and ulcerated duodenal diverticulum (1). Two of these patients rebled (the jejunal A–V malformation and the ulcerated duodenal diverticulum), the former needing a right hemicolectomy. Two patients had a right hemicolectomy and excision of small bowel A–V malformations. Neither has rebled.

In 71 patients there were 16 lesions, 13 diagnosed and three undiagnosed, other than angiodysplasia. Angiodysplasia bled on two occasions after the removal of a specific small bowel lesion. Thus, in the 40 patients with angiodysplasia who came to surgery, 16 (40 per cent) had a second lesion and four (10 per cent) required further surgery.

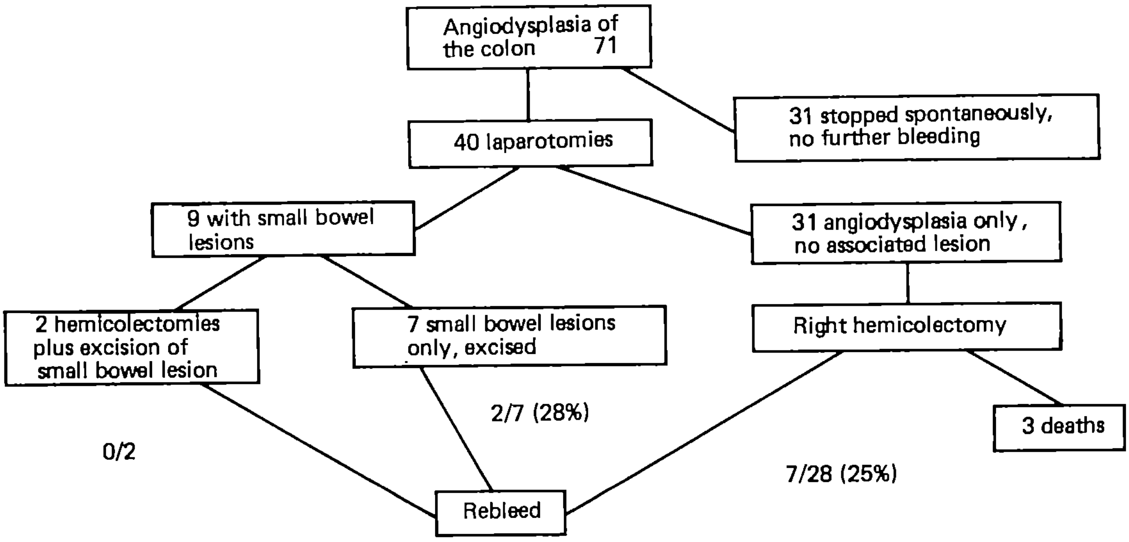
Angiodysplasia of the colon 71
31 stopped spontaneously, no further bleeding
40 laparotomies
9 with small bowel lesions
31 angiodysplasia only, no associated lesion
2 hemicolectomies plus excision of small bowel lesion
7 small bowel lesions only, excised
Right hemicolectomy
2/7 (28%)
3 deaths
0/2
7/28 (25%)
Rebleed

Figure 1 *Flow chart showing management and outcome of 71 patients with proven colonic angiodysplasia*

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Discussion

Angiodysplasia in association with Meckel's diverticulum has been previously reported[5] as has a re-bleeding rate of 19 per cent[4] after surgery for colonic angiodysplasia. In this review, however, 13 out of 71 patients had a definite second lesion and three a presumed second lesion.

Treatment options depend on the significance of the angiodysplasia, whether it is seen to be actively bleeding or not, and of the second lesion. This may be large and isolated (ileal carcinoid or Meckel's diverticulum) or small (jejunal A–V malformation). The options are to remove either the angiodysplasia or the small bowel lesion, or to remove both. In our series, the first two options were associated with a 25 per cent re-bleeding rate, i.e. from remaining angiodysplasia or other gastrointestinal tract lesions. The numbers under discussion are small, but neither of the patients who had both lesions removed have rebled. If there is any doubt about angiodysplasia as a cause of bleeding and a significant second lesion is found, the latter alone can be removed. If the angiodysplasia causes problems subsequently, it could be treated colonoscopically with electrocoagulation or laser[6] and resection avoided. To leave a small bowel lesion (e.g. an A–V malformation) may be to leave a lesion of little significance but one that can only be treated by resection at further laparotomy.

In view of the high association of small bowel lesions with angiodysplasia, a thorough laparotomy should be performed if a patient undergoes surgery, with a view to right hemicolectomy for proven colonic angiodysplasia. If a second lesion is found, we recommend that it should be removed. If the angiodysplasia has been seen to be bleeding at colonoscopy or angiography, that too should be removed. On the other hand, since angiodysplasia may be asymptomatic[7,8], if these lesions have never actually been seen to be bleeding, an expectant policy may be adopted.

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Announcement

Overseas Doctors Training Scheme (Surgery)

At the request of the Department of Health and Social Security (DHSS), the Royal College of Surgeons of England is setting up a training scheme in general surgery and orthopaedics for doctors from abroad. This will be under the arrangements for double sponsorship introduced by the General Medical Council. The posts included in the scheme will be established National Health Service posts subject to the DHSS Terms and Conditions of Service and with Royal College recognition. In the main overseas doctors will be appointed to rotational programmes of surgical training, where possible including University Teaching Hospitals, in regions throughout England and Wales, and Northern Ireland. The principle aim of this scheme is to provide a high standard of surgical training for doctors outside the United Kingdom and the European Community to help them in their work when they return home. Further particulars can be obtained from the ODTS office, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK.

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Percutaneous transhepatic cholangioscopy

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Since 1983, percutaneous transhepatic cholangioscopy has been performed in 50 patients for both therapeutic and diagnostic purposes. Percutaneous transhepatic cholangioscopy was used to evaluate the nature of obstructive jaundice in 15 patients and bile duct stones were removed in 35 patients, 27 of whom also had intrahepatic duct stones. The overall success rate for stone removal was 80 per cent. Complications were few with no mortality. Emergency surgery was necessary in two patients, one for subphrenic haematoma, the other for a bile leak. Percutaneous transhepatic cholangioscopy is an effective and safe method for management of biliary stones and is a useful procedure for establishing the diagnosis of obstructive jaundice.

Keywords: Percutaneous transhepatic biliary drainage, choledochoscope, obstructive jaundice, retained biliary stones

In patients with obstructive jaundice, percutaneous transhepatic biliary drainage (PTHBD) has afforded a satisfactory alternative to surgery for palliative biliary drainage. It can also be used to provide temporary decompression before surgery[1–8]. Operative mortality after emergency open surgical procedures for severe acute cholangitis is still very high[9–15], PTHBD procedures can be lifesaving in biliary sepsis[4,6]. Thus, percutaneous transhepatic catheterization techniques may provide a way to approach hepatobiliary problems[1–17]. Percutaneous transhepatic cholangioscopy (PTCS) was first introduced by Nimura *et al.* in 1981[18], as one of the alternatives in dealing with hepatobiliary disease. It consisted of: PTHBD, dilatation of PTHBD fistula and insertion of a fibreoptic choledochoscope via the fistula tract. This paper presents our experience with the PTCS for diagnostic and therapeutic purposes.

Patients and methods

In the period June 1983–June 1986, at the LinKou Medical Centre, Chang Gung Memorial Hospital, PTCS was performed in 50 patients[19]. There were 33 men and 17 women. Age ranged from 24 to 85 years with a mean of 45 years. Of the 50 patients, 35 were found to have biliary stones (PTCS was performed for the removal of retained or reformed stones) and 15 were found to have non-calculous bile duct obstruction and in each case PTCS was undertaken to diagnose obstructive jaundice.

Indications for PTCS

Stone removal. Percutaneous transhepatic catheterization and drainage was done because of biliary colic, obstructive jaundice and cholangitis[19]. Of the 35 patients, 24 had a previous history of repeated biliary tract operations. Four were considered a poor risk because of advanced age and seven were treated in association with septic shock.

Investigation of obstructive jaundice. In selected patients with obstructive jaundice, choledochoscopy was performed after temporary decompression.

Table 1 *Liver function tests of 15 patients with obstructive jaundice (non-calculous)*

	Mean	Range
Albumin (g/dl)	3·0	(2·5–3·8)
Bilirubin, total (mg/dl)	15·4	(2·7–32)
S-GOT (milliunits/ml)	355·0	(85–1250)
S-GPT (milliunits/ml)	210·0	(55–880)
Alk-P (milliunits/ml)	355·5	(125–550)

Technique

Standard percutaneous transhepatic cholangiography was performed in all patients to identify the bile ducts[19]. The right intrahepatic bile duct was entered with a stylet and sheath from the right mid-axillary line. When a left duct approach was required, the inferior segmental duct of the left lateral lobe was entered. After the sheath had been advanced into the hepatic duct, a guidewire was inserted into the bile duct and the sheath was removed. A suitable sized catheter, usually an 8–12 Fr. Teflon, was introduced into the hepatic duct via the guidewire. The guidewire was removed, but the catheter remained in the bile duct. The drainage catheter was attached firmly to the abdominal wall by a stay suture and was connected to a drainage bottle.

Dilatation of the percutaneous transhepatic biliary drainage fistulae was performed by re-insertion of a guidewire, and a bigger sized catheter was introduced for 1 week until a suitable sized fistula tract (18–20) Fr.) was formed. This usually requires repeated dilatation over 4 weeks, after the initial introduction of non-operative biliary drainage.

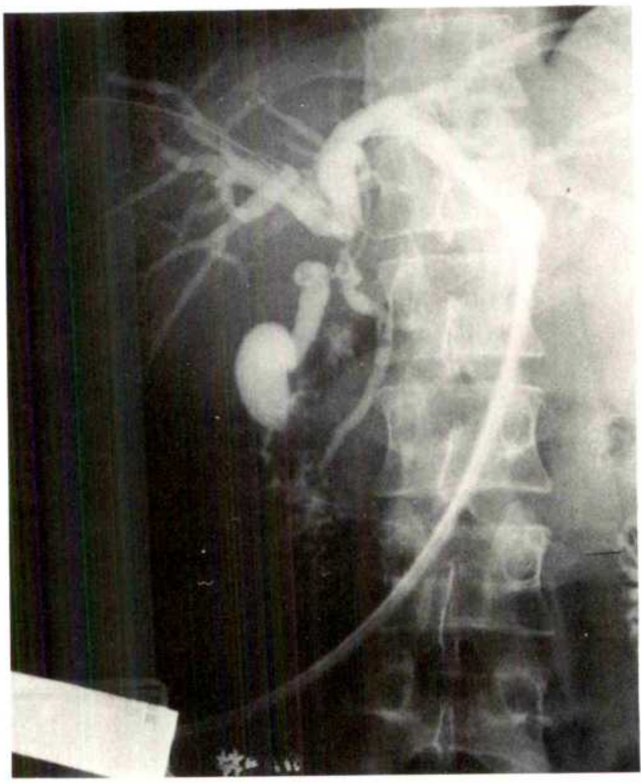

Figure 1 *Percutaneous transhepatic biliary drainage of a patient with carcinoma of common hepatic duct (case 1,* Table 2)

Fiberoptic choledochoscopy for stone removal was performed in the out-patient clinic. With the patient in the supine position, the skin was prepared with povidone–iodine and draped aseptically. The non-operative biliary drainage tube was then removed and the Olympus choledochofiberscope CHF B4 was inserted via the orifice of the fistula. Physiological saline solution was run into the intrahepatic ducts and common bile duct through the instrument's irrigation channel. If biliary stones were visualized, grasping forceps were applied. Stones could then be caught in the basket of the forceps under direct vision. Another catheter (or drainage tube) was introduced into the fistula to maintain patency for possible repetition of the procedure. Most of the patients tolerated the cholangioscopy without medication. When necessary, 50 mg pethidine was given intramuscularly. Ampicillin was prescribed for 3 days afterwards (500 mg orally every 6 h). If no further cholangioscopy was required, the catheter tube was removed.

In patients with obstructive jaundice the cholangioscope was used to visualize the obstruction and to biopsy the lesion.

Results

PTCS for removal of biliary stones

Altogether 115 PTCSs were performed on the 35 patients with biliary stones. Left ducts were entered in 29 patients, and right ducts in 6 patients. Biliary stones were completely removed in 21 out of 27 patients with intrahepatic duct stones and in 7 out of 8 with common bile duct stones. The removal of all stones was evaluated visually at the end of endoscopy, or by cholangiography performed through the sinus tract. Overall success rate was 80 per cent. For stones lodged in the common bile duct the success rate was 87·5 per cent and for intrahepatic duct stones it was 77·7 per cent. In only one patient did the method fail to remove any stone. Repetition of PTCS was required in most cases, the average number of performances per patient being 4·3 (range 1–12).

Complications were few; there was no mortality. One patient developed fever and chills after PTCS, and these responded to nasogastric suction, intravenous administration of fluids and antibiotics. Two patients needed an emergency laparotomy, one developed subphrenic haematoma and the other a bile leak after percutaneous punction of the right ducts.

PTCS for obstructive jaundice

PTCS was performed in 15 patients with obstructive jaundice caused by non-calculous lesions (*Table 1*, *Figure 1*). There were four with adenocarcinoma of the common bile duct, three with cancer of pancreatic head, two with adenocarcinoma of the ampulla of Vater, two with metastasis of gastric carcinoma. Chronic pancreatitis, chronic cholangitis, benign stricture of common bile duct, and stricture of hepaticojejunostomy were found, each in one patient. The endoscopic findings which contributed to the diagnosis of malignancies were intraluminal tumour growths, polypoid or nodular masses, infiltrative lesions with or without mucosa erosion. Sometimes, diagnosis of extrinsic compression of the common bile duct can be made due

Table 2 *Diagnosis of 15 patients with non-calculous bile duct obstruction*

Case no.	ERCP or PTC diagnosis	PTCS finding	Biopsy	Laparotomy	Final diagnosis
1	Hilar tumour	Intraluminal tumour with obstruction at hilum and IHD	Adenocarcinoma	–	Cholangiocarcinoma, common hepatic duct
2	Hilar tumour. r/o IHD stone	a) Sclerosing type obstruction (rigid, extensive infiltrative) mucosa seemed intact b) Stones in CBD, IHD	Adenocarcinoma	+	Cholangiocarcinoma, common hepatic duct
3	CBD cancer	Sclerosing type obstruction hilum	Inflammation	+	Cholangitis
4	Periampullar tumour	Intraluminal polypoid mass, distal CBD	Adenocarcinoma	+	Adenocarcinoma papilla of Vater
5	CBD cancer. r/o stone	Intraluminal polypoid mass, CBD	Adenocarcinoma	+	Adenocarcinoma CBD
6	Pancreatic head carcinoma	Extrinsic compression CBD, normal mucosa	Nil	+	Chronic pancreatitis
7	Pancreatic head carcinoma	Extrinsic compression atrophic mucosa	Inflammation	+	Pancreatic head carcinoma
8	Gastric carcinoma with metastasis	External compression with normal mucosa CBD	Nil	–	Gastric carcinoma metastasis
9	Malignant CBD obstruction	Intraluminal nodular mass, CBD, r/o extrinsic compression	Inflammation	+	Pancreatic head carcinoma with bile duct involvement
10	Benign stricture of CBD	Stricture of CBD, extraluminal lesion (?)	Inflammation	+	Benign stricture of CBD
11	Stricture of biliary–enteric anastomosis	Stenosis of hepaticojejunostomy	Nil	–	Stricture of hepatico-jejunostomy
12	Gastric carcinoma with metastasis. r/o stone	Stenosis of CBD, r/o extralumina lesion	Nil	+	Gastric carcinoma metastasis
3	R/o pancreatic head carcinoma	External compression, CBD, stenosis of CBD	Nil	+	Pancreatic head carcinoma
4	Periampullar tumour	Polypoid mass, distal CBD with mucosa destruction	Adenocarcinoma	+	Papilla of Vater adenocarcinoma
5	Hilar tumour	Stricture sclerosing of CBD	Adenocarcinoma	+	Carcinoma common hepatic duct

HD, intrahepatic duct; CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; TC, percutaneous transhepatic cholangiography to a bulging mass with intact or smooth mucosa. Histopathological confirmation of 'adenocarcinoma' was found in six patients, by taking specimens under direct vision via the endoscope (*Table 2*).

The complication rate of PTCS for obstructive jaundice was low without mortality. Two patients developed transient haemobilia which disappeared after irrigating the bile duct with normal saline solution.

Discussion

With the aid of choledochoscopy, diagnosis can be made under direct vision via the endoscope and confirmed by biopsy. In addition, PTCS makes it possible to differentiate whether the cause of obstructive jaundice is benign or malignant, to determine the extent of involvement, and also to detect multiple foci before operation[18]. Biopsy performed in conjunction with percutaneous transhepatic biliary drainage procedures can often provide a definite diagnosis. Voegeli and his colleagues, in 1985, concluded that final tissue diagnoses were made in 20 out of 23 patients (87 per cent) by transcatheter or percutaneous biopsy[20]. It is probable that, with the aid of cholangioscopy, a higher percentage of definite diagnoses can be made.

Percutaneous transhepatic fiberoptic choledochoscopy can be used as an alternative approach to removal of biliary stones. In this series, retained or reformed stones after choledochotomy were removed from 35 patients by means of the PTCS. Complete stone removal was achieved in 28 patients (21 with intrahepatic duct stones and 7 with common bile duct stones). The percutaneous technique is preferred for high risk patients, or for stones which have reformed after various biliary-enteric anastomoses. Using basket forceps and balloon-tipped catheters under direct visual control, choledochoscopy avoids the sometimes lengthy irradiation of the patient that is required for extraction of stones under fluoroscopic guidance. Moreover, fiberoptic choledochoscopy permits accurate visualization of calculous-suspect radiological defects, so that air bubbles and blood clots in the biliary tree are not mistaken for stones[18,19].

A tortuous and narrow tract may sometimes be difficult to negotiate with a choledochofiberscope[21-23]. To overcome this problem, the left duct approach is preferable and the fistula tract should be dilated. It is necessary to dilate to at least Fr. 18 sized fistula[24]. The relatively long hospital stay required, involving repeated and often time-consuming intervention has been well tolerated by the patients.

Percutaneous transhepatic removal of common bile duct and intrahepatic ducts stones was performed because the patients were unwilling to have further surgery, or were of advanced years and/or were a high risk for surgery. The complications of percutaneous transhepatic cholangioscopy were few, and these were only recorded in percutaneous transhepatic biliary drainage[5-8]. Considering the complications of open operation, percutaneous intervention is an attractive alternative to surgery in selected patients.

In conclusion, PTCS can be used as an effective and safe procedure to remove retained or reformed biliary stones after choledochotomy, and its diagnostic value in the definite diagnosis of obstructive jaundice in particular patients is also confirmed.

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Loss of substance in bile ducts treated by a new surgical endoprosthesis

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Three cases of loss of substance of the common bile duct in patients with neoplastic disease treated by a new surgical endoprosthesis are reported. In all patients a good biliary drainage was obtained without a biliary fistula. There were no complications related to this method. Long-term follow-up showed persistence of the good immediate results. Surgical endoprostheses might be an alternative in cases with peroperative loss of substance of the common bile duct in patients with neoplastic disease to hepato-enteric anastomoses.

The treatment of a loss of substance of the extrahepatic biliary ducts is difficult, especially if the defect is situated near the confluence and if the intrahepatic ducts are small[1,2]. A bilio-enteric anastomosis performed on small ducts is exposed to recurrent stricture and cholangitis. Furthermore, this kind of anastomosis should not be performed next to an unresectable cancer, even when the intrahepatic ducts are dilated, because umour spread may compromise its function[3].

We have treated three patients with hilar lesions with loss of substance of the common bile duct by using a new biliary endoprosthesis placed surgically. This procedure allowed reatment while avoiding the discomfort due to the change of the endoprosthesis sometimes necessary with an endoscopic or percutaneous approach.

Patients and methods

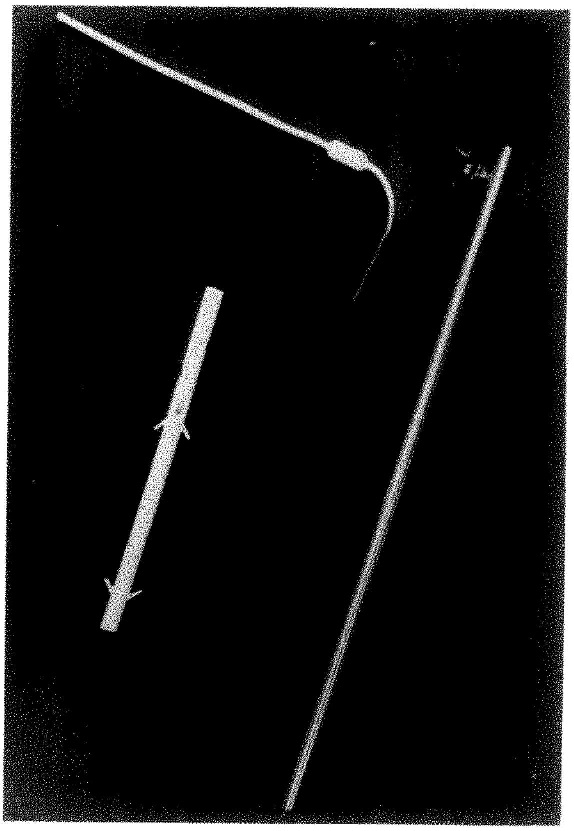
Material

The endoprosthesis (*Figure 1*) combines a special silicone moulded body einforced by a metal spiral spring capable of resisting tumour compression. Superior and inferior barbs avoid migration. The prosthesis exists in all sizes from 10 to 18 French and each size comes in wo different lengths. A flexible mandrel helps insertion of the endoprosthesis. This endoprosthesis has shown excellent tolerance when used as a replacement of the common bile ducts in dogs. During a 1-year follow-up, there were no episodes of cholangitis or histological hanges in repeat liver biopsies[4]. This has now been confirmed by our linical experience which includes more than 25 patients[5].

Patients

Case 1. A 61-year-old man developed liver metastases in the right obe 5 months after left hemicolectomy for adenocarcinoma. A right hepatectomy was performed together with resection of Segment I and emoval of a metastasis in Segment IV. During surgery, a small injury to he common bile duct was sutured with resorbable material. The ubhepatic space was drained. The postoperative course was marked by n increased serum bilirubin concentration following the eighth postoperative day, and an external biliary fistula via the drain. A retrograde cholangiography 1 month after operation showed a tricture of the common bile duct from which originated the fistula. However, the hilar and intrahepatic ducts were not dilated. Ultrasound onfirmed these lesions. Bilirubin level was 250 μmol/l, and alkaline hosphatase was 331 units/l (normal <82 units/l). Relaparotomy was performed on the 40th day, and a biliary fistula was displayed t the site of the common bile duct suture. The intrahepatic ducts were ot dilated, but the common duct was strictured over a length f 2 cm. After splitting the stricture, only the posterior wall of the ommon duct remained. A 10 French endoprosthesis was inserted, intubating the left hepatic duct and the common bile duct below the tricture. The common bile duct could not be sutured over the endoprosthesis, and the region was drained via a subhepatic drain. The postoperative course was uneventful, and the drain was taken out on the fifth postoperative day. One month after relaparotomy, the bilirubin level was 33 μmol/l and alkaline phosphatase was twice normal. In spite of recurrent hepatic and pulmonary metastases, this patient remains well without jaundice, pruritus or cholangitis 33 months postoperatively and is receiving intravenous chemotherapy. Present liver function tests show a normal bilirubin level with slightly elevated alkaline phosphatase.

Case 2. A 78-year-old woman underwent cholecystectomy and common bile duct exploration for cholecystolithiasis associated with obstructive jaundice. Peroperative cholangiography showed a stricture of unknown nature at the origin of the cystic duct from which a biopsy



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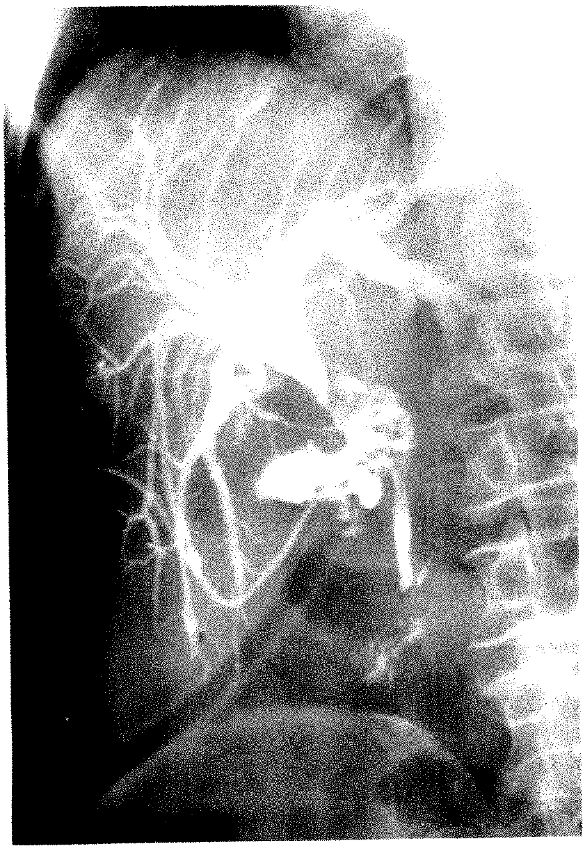

Figure 2 *T-tube cholangiogram of case 2 showing leak stricture*

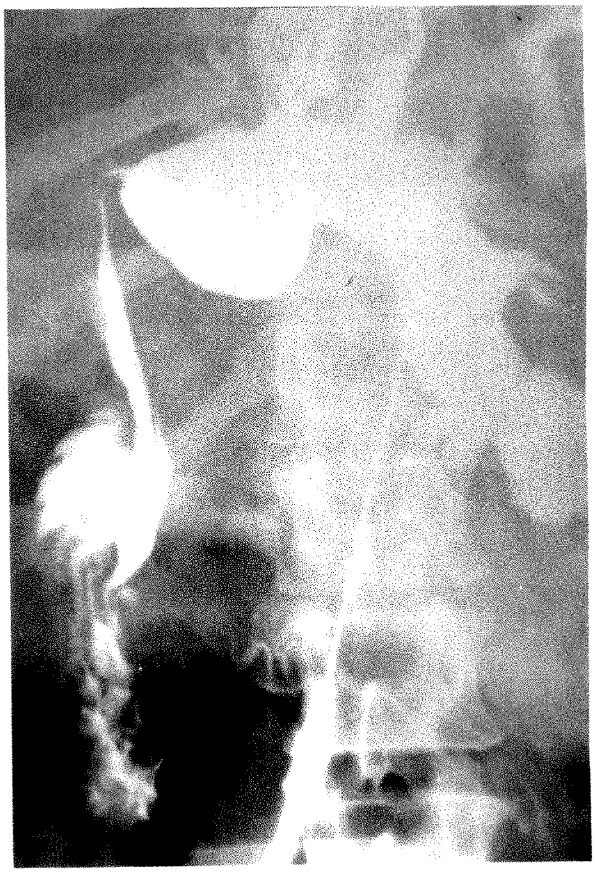

Figure 3 *Percutaneous cholangiogram of case 3 showing long stricture*

was taken. There were no common duct stones. The common bile duct was drained by a T-tube. Histology showed a gallbladder carcinoma invading the cystic duct. The patient was then referred to our institution with persistent jaundice due to a bilirubin level of 273 μmol/l. Cholangiography via the T-tube showed a biliary leak and a tight stricture of the common bile duct. The intrahepatic ducts were moderately dilated (*Figure 2*).

At reoperation, the common duct was found to be strictured at the site of the T-tube and, after taking out the tube, a loss of substance from the anterior wall was apparent. An 18 French endoprosthesis was inserted into the left duct, descending to the lower common duct. The subhepatic space was then drained. The postoperative course was uneventful, and the subhepatic drain was taken out on the fifth postoperative day. The patient left hospital on the 17th postoperative day with a bilirubin level of 42 μmol/l. The patient is reviewed regularly and is well without jaundice or pruritis at 13 months follow-up.

Case 3. A 55-year-old man was admitted to our institution with jaundice and cholangitis, together with a weight loss of 7 kg in 2 months. Ultrasound showed marked dilatation of the left hepatic ducts, whereas the right lobe had a heterogeneous texture without dilatation of the right ductal system. A tumour of the right lobe was diagnosed with extension to the origin of the left duct. The bilirubin level was 402 μmol/l and alkaline phosphatase was 4·5 times the normal level.

An exploratory laparotomy revealed diffuse peritoneal carcinomatosis, an atrophic left and a hypertrophic right lobe. The right lobe contained multiple large tumours, whereas the left lobe contained several small tumours. Frozen section showed these tumours to be adenocarcinomas, which were thought to be secondaries from a digestive tract tumour. The primary tumour was not discovered during laparotomy. Cholangiography by direct puncture of the Segment III duct (*Figure 3*) showed marked dilatation of the left hepatic ducts, with a tight stricture at the confluence and the common duct over a length of 3 cm. There was no filling of the right ductal system. The stricture was treated by direct splitting, dilatation and intubation with an 18 French endoprosthesis, leaving a large defect in the anterior wall of the left hepatic duct. The subhepatic space was then drained. The postoperative course was uneventful and the subhepatic drain was taken out on the eighth postoperative day.

The hospital stay was 15 days. Regular follow-up showed a satisfactory decrease in bilirubin and alkaline phosphatase levels. The patient died 3 months after surgery without recurring jaundice or pruritus.

Discussion

The surgical treatment of a neoplastic or inflammatory stricture of the bile ducts may require its splitting in selected cases, thus leading almost automatically to a loss of substance. Percutaneous and/or endoscopic treatment of this kind of stricture has been attempted to avoid surgery and its consequences, including such exceptional loss of substance in the bile ducts. However, the immediate and long-term results of these techniques appear unsatisfactory.

The success rate for endoscopic intubation in hilar strictures is lower than for distal strictures, and successful stenting may need a combined endoscopic and percutaneous approach. Although percutaneous intubation seems more successful in hilar strictures, its immediate complication rate is higher than that of endoscopic intubation. With both techniques, repeat changes of the endoprosthesis are often necessary in the long-term because of obstruction and cholangitis[6,7].

The only surgical alternative to these methods until now has been either a bilio-enteric anastomosis using the Segment III duct or a Roux-en-Y loop anastomosed to the confluence. However, the first requires a dilated left intrahepatic duct[1,2] which was not the case in two of our patients. Furthermore, the presence of hepatic metastases usually excludes the possibility of an intrahepatic bypass. The second method is not advisable when the anastomosis has to be performed next to a tumour[3], which was the case in two patients (cases 2 and 3).

The clinical experience in the treatment of neoplastic strictures of the bile ducts with the surgical endoprosthesis described here has resulted in a good quality of life and an excellent tolerance of the endoprosthesis[5]. The operative technique is simple and carries a low morbidity and mortality rate.

We report here three patients with loss of substance of the extrahepatic bile ducts, where the endoprosthesis permitted adequate internal drainage without the necessity of an anastomosis or external drainage. All three had good results and remained free from cholangitis, jaundice or pruritus. There was no morbidity nor mortality related to this method. In all cases, the bile duct could not be closed over the endoprosthesis requiring drainage of the subhepatic space. We consider this drainage mandatory, because of a constant but transient biliary leak. The drain could always be taken out between the fifth and eighth postoperative day.

These cases confirm the experimental studies of Bradley *et al.*[8] and Kron[9] showing that loss of substance in the extrahepatic bile ducts can be replaced when a leading tube is left in place in the extrahepatic bile ducts. The use of an endoprosthesis for loss of substance in the extrahepatic bile ducts seems to be particularly valuable in patients with neoplastic hilar lesions[10,11] that cannot be resected and where survival is limited. However, this method does not yet apply to the treatment of benign strictures, even with a loss of substance, which should not be treated with a surgical endoprosthesis until the device has proven its perfect tolerance in long-term follow-up studies.

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Announcement

Reviews

The Editorial Board of *The British Journal of Surgery* continues to invite review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium of £100. Potential authors seeking advice on the suitability of review topics are advised to contact: Professor D. C. Carter, University Department of Surgery, Royal Infirmary, Glasgow G31 2EU, UK.

Leading articles

The Editors invite submissions of signed leading articles to *The British Journal of Surgery*. These articles should be 600–1000 words in length, should address controversial topics of current interest and should be supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium of £100 is payable on publication. Potential authors seeking advice on the suitability of topics are advised to contact: Professor D. C. Carter, University Department of Surgery, Royal Infirmary, Glasgow G31 2EF, UK.

Surgical workshops

The Editors invite the submission of articles describing technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they can be accompanied by no more than two figures but should not carry supporting references. Articles submitted to the Surgical Workshop series may be subjected to external review and assessment by the Editorial Board before acceptance.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is likely to be high. Authors are advised to restrict such reports to a maximum of 500 words, to use no more than five references and to submit no more than one illustration.

Br. J. Surg. 1987, Vol. 74, August, 734–735

Suture materials in contaminated wounds: a detailed comparison of a new suture with those currently in use

The relationship between five different suture materials (expanded polytetrafluoroethylene (PTFE), polypropylene, polyglycolic acid, polydioxanone and polyglactin 910) and infection has been studied in 540 guinea-pig wounds contaminated with synergistic enteric organisms. The recently introduced expanded PTFE suture has been studied because, unlike the others, it has not previously been studied under these contaminated conditions. The incidence of wound infection in the control series was 26 per cent and all suture materials increased this figure significantly. The infection rate using expanded PTFE of 51 per cent was similar to all other sutures except polyglycolic acid, which produced an infection rate of 41 per cent. This difference was not statistically significant at the 5 per cent level. This confirms other studies including our own which show that the presence of most suture materials in contaminated wounds increases the incidence of infection. It further demonstrates that expanded PTFE is no different from other materials in this regard.

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Keywords: Contaminated wounds, suture materials

The introduction of antibiotic prophylaxis in contaminated abdominal surgery has reduced the wound infection rate to below 10 per cent in most cases[1–4]. Several studies have demonstrated that the different properties of suture materials contribute to wound infection, with braided and naturally occurring materials, such as catgut, having higher sepsis rates than monofilament sutures[5–8].

The recently introduced expanded PTFE (GORE-TEX)* material is regarded as one of the most inert and tissue compatible of all the biomaterials currently available. It is not biodegradable, but incorporates interstices which allow it to become integrated into the surrounding tissue. Expanded PTFE has been used for synthetic vascular prosthesis and is now available in suture form.

We have investigated the behaviour of expanded PTFE sutures in guinea-pig wounds contaminated with synergistic enteric bacteria (*Escherichia coli* and *Bacteroides fragilis*), and compared it to that of others commonly used; polyglactin 910 (VICRYL)†, monofilament polydioxanone suture (PDS), polypropylene (PROLENE)† and polyglycolic acid (DEXON)‡. If expanded PTFE sutures are to become more widely used then this knowledge is essential.

Materials and methods

The animal model used was based on that first described by Kelly in 1980[9], using female guinea-pigs weighing 400 g. Under ether anaesthesia, the dorsum of the animal was shaved and prepared with chlorhexidine in 70 per cent alcohol and six subcutaneous pouches were fashioned. After insertion of the suture, or in the control the passage of a needle through the deep fascia, 5×10^5 organisms of both *E. coli* and *B. fragilis* in 0·5 ml normal saline were inoculated into the wounds before closure with 2 Michel clips. The wounds were inspected after 7 days, when the animals were killed by an injection of intraperitoneal pentobarbitone. Assessment of the wounds was performed by a single observer under 'blind' conditions. Wounds which produced frank pus or copious exudate were considered infected.

The infection rates between different sutures and between sutures and control were compared using the χ^2 test.

Bacteriological methods

Pure cultures of *E. coli* and *B. fragilis* were obtained by selective culturing and sub-culturing a specimen of pus taken from a patient with an intra-abdominal abscess. They were stored separately in 10 per cent glycerol broth at −70°C until required. When required the *E. coli* was grown in Brain Heart Infusion Broth and the *B. fragilis* in Fastidious Anaerobe Broth (LabM, Salford UK) both for 24 h at 37°C. Serial tenfold bacterial dilutions were made in normal saline to obtain the correct number of organisms. Bacterial counts were checked by surface viable counting on MacConkey agar plates incubated aerobically (for *E. coli*) or on blood agar plates incubated anaerobically using the Gaspak System (BBL Microbiology Systems, Becton Dickinson and Co., Maryland, USA) for *B. fragilis*.

Results

A preliminary study was carried out using 12 animals (72 wounds) without sutures and with varying numbers of bacteria in order to produce an infection rate of around 30 per cent. This is similar to that figure seen in man following contaminated abdominal surgery without antibiotic chemoprophylaxis. The number of organisms required was 5×10^5 for each species.

Ninety guinea-pigs were studied, providing 540 pouches for analysis. No guinea-pigs died during the operation, although four died within the 7 days, and these were not included in the analysis. The infection rates of each material used are shown in *Table 1*.

Bacterial specimens from the wounds were not taken, as a previous study from this department has shown that bacteria can be demonstrated in most wounds, irrespective of overt

Table 1 *The suture related wound infection rate*

Material	Infection (out of 90)	Percentage
Control	23	26
PROLENE	47	52
VICRYL	48	53
DEXON	37	41
GORE-TEX	46	51
PDS	47	52

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* GORE-TEX is a trademark of W. L. Gore and Associates Inc.
† PDS, VICRYL are trademarks of Ethicon Ltd
‡ DEXON is a trademark of Davis and Geck

infection[7]. We relied solely on the clinical assessment of the wounds to determine infection rates.

Discussion

Before antibiotic prophylaxis was introduced, surgery on the gastrointestinal tract, in particular on the colon and rectum, was associated with wound infection rates of 10–60 per cent[4,10,11]. After the introduction of perioperative antibiotic administration, the incidence has been reduced to below 10 per cent in most cases[1–4], although wound infection in severely contaminated cases (e.g. perforated appendicitis) is frequent[12,13]. The persistence of wound infections in spite of chemoprophylaxis is related, apart from the severity of contamination, to the presence of ischaemic tissue and foreign bodies in the wound[14,15] and one of the commonest of these is the suture inserted by the surgeon during wound closure. It has been shown in experimental studies that braided materials can significantly increase this wound infection rate[5–9], which is thought to be directly related to their high capillary property. The bacteria enter the interstices of the suture, where they multiply in relative safety from the surrounding inflammatory response[16]. Katz and colleagues[6] examined this further, both with radiolabelled bacteria and scanning electron microscopy. Bacterial adherence to braided sutures was five to eight times that of monofilament nylon and correlated with the incidence of infection. The degree of inflammatory reaction produced may also be a contributory factor, with catgut and braided sutures resulting in a more severe reaction than monofilament material[5,17]. Previous studies from our unit further investigated this relationship between sepsis and currently used synthetic suture material in contaminated wounds[7,8] confirming the increased infection seen with chromic catgut and showing that this also occurred with braided nylon (polyamide 66) and braided polydioxanone (PDS). Monofilament PDS, polypropylene (PROLENE), polyglycolic acid (PGA = DEXON) and silk however did not significantly increase the rate of wound infection. This last finding was surprising as others have shown silk to be associated with an increased infection rate[5,6,17]. Likewise we were unable to reproduce our own previous studies, as in this study all sutures increased the wound infection rate, although the difference between control and PGA was only significant at the 5 per cent level, whereas it was significant at the 1 per cent level when compared with all the other sutures. The difference in infection rates between PGA and the other materials is not significant ($P < 0.05$).

There is no doubt that this study is open to criticism in the interpretation of the infected wounds. Some might argue that a scoring system would be more appropriate, but this is difficult and would include a 'grey area' between infected and nonnfected wounds. We felt that by accepting one extreme of the scale as 'infected', a finite measurement could be made. By producing a control infection rate of 26 per cent, similar to that seen in the other studies, limited comparison may be made. We cannot explain why sutures which did not significantly increase nfection rate in the previous studies did so in ours, and therefore he only conclusions which can be made are that all sutures ncrease infection in wounds contaminated with synergistic enteric organisms and that the recently introduced expanded PTFE suture behaves in a similar manner to all other sutures under these conditions.

Acknowledgements

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Lateral paramedian incision

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Prospective randomization of 360 patients undergoing abdominal surgery determined whether a standard lateral paramedian incision was made (group A) or one of two modifications in which the anterior sheath was incised medially and posterior sheath incised laterally (group B) or vice versa (group C), in order to determine the necessity for incising both layers laterally to provide the shutter mechanism which is held responsible for the integrity of this wound. Medial incision of the anterior rectus sheath significantly reduced the time required to perform the incision ($P<0.02$) *and tended to reduce wound sepsis rate. However, this was achieved at the cost of a higher incisional hernia rate (0 per cent, 2·9 per cent and 4·6 per cent in groups A, B and C respectively,* $P<0.02$*). We conclude that lateral incision of both anterior and posterior rectus sheath is necessary to obviate the risk of wound hernia with the lateral paramedian incision.*

Keywords: Lateral paramedian incision, incisional hernia

In 1980 we described a modification of the paramedian incision in which the anterior and posterior rectus sheaths were incised just medial to the lateral border of the sheath in the hope that the wide shutter mechanism this provides would diminish the incidence of wound dehiscence and incisional hernia. Superiority of this approach over conventional paramedian and mid-line incisions was demonstrated by clinical trial[1] and subsequently it was demonstrated that the intrinsic strength of lateral paramedian incision was independent of the material employed to suture it[2]. Our confidence in this incision was confirmed in over 850 documented cases with no wound dehiscences and an incisional hernia rate of less than 0·4 per cent over a minimum follow-up period of 12 months[3]. Furthermore, a recent independently conducted clinical trial[4] confirmed the excellent results which may be expected with this incision.

However, the lateral paramedian incision possesses two drawbacks which may render it unacceptable to some surgeons. Firstly, it unquestionably takes longer to perform than conventional incisions as a consequence of the extensive dissection of the rectus muscle from the anterior sheath. This makes it inappropriate for cases with life-threatining haemorrhage and may also explain the second disadvantage, namely the higher incidence of wound infection we observed with this incision in our original trial. Both disadvantages might potentially be overcome if it could be demonstrated that it was unnecessary to divide both the anterior and posterior sheaths laterally such that one lateral layer would suffice to provide the shutter mechanism.

In an attempt to determine which is the important layer we conducted a prospective randomized controlled clinical trial in which we compared our standard lateral paramedian incision with the same incision but with either the anterior or posterior sheath incised medially. By so doing we hoped to determine whether or not it is important to incise both layers laterally and, if not, which one provides the incision with its inherent strength.

Patients and methods

From March 1981 to March 1984 all patients admitted for elective and emergency abdominal surgery other than life-threatening haemorrhage were considered for this study. Patients with previous vertical abdominal incisions or other incisions which might encroach on the proposed wound were excluded. Sixty-eight such patients presented for laparotomy, having had such incisions, and these patients were not considered for further follow-up. During this time 360 patients were prospectively randomized to undergo either the standard lateral paramedian incision as previously described[1] (group A) or one of two modifications (groups B and C). In group B patients the anterior rectus sheath was incised vertically at a point 2 cm from the mid-line and, after mobilization of the rectus abdominis, the posterior rectus sheath was incised vertically at a point just medial to the lateral border of the rectus sheath as for the standard lateral paramedian incision. In contrast, patients in group C underwent a standard lateral incision of the anterior sheath, dissection of the rectus muscle and incision of the posterior sheath 2 cm from the mid-line. Patients were randomized to groups A, B or C using a blind card system at the induction of anaesthesia. At completion of the operative procedure all wounds were closed with continuous No. 1 chromic catgut to the posterior rectus sheath, continuous No. 1 Prolene to the anterior rectus sheath and interrupted silk sutures to the skin. Tension sutures were not used and drains were brought out through separate incisions.

For each patient a standard pro forma was completed which contained details of age, sex, diagnosis, operative details, past medical history, haemoglobin and albumin levels. Prophylactic antibiotics were administered where indicated. This included the majority of cases and were continued for a minimum of 48 h postoperatively. Wounds were examined daily and sutures removed on the day a firm healing ridge was palpable. Significant wound infections were defined as those giving rise to the generation of culture-positive pus which delayed the patient's discharge from hospital. The presence of a deep or superficial wound dehiscence was also noted. All wounds were further examined at 1, 3, 6 and 12 months after operation. At each visit presence of any incisional hernia was recorded. All patients were followed for at least 1 year.

Results

From March 1981 to March 1984 360 patients were randomized to undergo one of the three incisions described. Nine patients were lost to follow-up and are not considered further leaving 119 patients in group A (true lateral paramedian incision), 115 in group B (medial anterior sheath, lateral posterior sheath) and 117 in group C (lateral anterior sheath, medial posterior sheath). During the initial 1 year follow-up period there were 14 deaths in group A, 11 in group B and 8 in group C.

Indications for surgery and relevant clinical details are shown in *Tables 1–3*, from which it is seen that there is no significant difference between the three groups with regard to factors which might predispose to abdominal wound dehiscence. As expected, time taken to perform the incision was significantly greater when a lateral dissection of the anterior rectus sheath was performed (A *versus* B, $t=9.2$, $P<0.02$; B *versus* C, $t=10.2$, $P<0.02$).

There were 25 significant wound infections in this study. Of these nine occurred in the standard lateral paramedian group (A, 7·6 per cent), five occurred in group B (4·3 per cent) and eleven in group C (9·4 per cent). Although these figures indicate a trend towards a higher rate of wound infection where a lateral dissection of the anterior rectus sheath was performed, this just fails to achieve statistical significance ($\chi^2=2.25$, P n.s.).

Table 1 *Patient details and indications for surgery*

	Group A	Group B	Group C
Mean age (years)±s.d.	55·3±20	57±23	56·1±19
Range (years)	14–87	11–85	19–87
M:F ratio	40:79	54:61	44:73
Elective cases	92 (77·3)	93 (80·9)	92 (78·6)
Acute cases	27 (22·7)	22 (19·1)	25 (21·4)
Biliary disease	57 (47·9)	38 (33·0)	51 (43·6)
Pancreatic disease	3 (2·5)	0	4 (3·4)
Peptic ulceration	23 (19·3)	18 (15·7)	16 (13·7)
Colorectal cancer	11 (9·2)	28 (24·4)	21 (18·0)
Small bowel obstruction	1 (0·8)	7 (6·1)	4 (3·4)
Inflammatory bowel disease	1 (0·8)	2 (1·7)	3 (2·6)
Gastric cancer	8 (6·7)	16 (14·4)	1 (0·9)
Appendicitis	1 (0·8)	2 (1·7)	3 (2·6)
Other	14 (11·8)	10 (8·7)	14 (12·0)
Total cancer	25 (21·0)	39 (33·9)	26 (22·2)

Values in parentheses are percentages

Table 2 *Pre-operative details*

	Group A	Group B	Group C
Cardiorespiratory disease	9 (7·6)	5 (4·4)	6 (5·1)
Diabetes	5 (4·2)	2 (1·7)	0
Jaundice	7 (5·9)	5 (4·4)	6 (5·1)
Uraemia	1 (0·8)	1 (0·9)	1 (0·9)
Steroids	2 (1·7)	2 (1·7)	2 (1·7)
Serum albumin <32 g/l	20 (16·8)	26 (22·6)	20 (17·1)
Mean Hb (g/dl)±s.d.	13·7±1·7	13·7±1·9	13·7±1·8

Values in parentheses are percentages

Table 3 *Peroperative details*

	Group A	Group B	Group C
Upper	97 (81·5)	75 (65·2)	75 (64·1)
Mid	11 (9·2)	17 (14·8)	19 (16·2)
Lower	11 (9·2)	23 (20·0)	23 (19·7)
Clean	20 (16·8)	21 (18·3)	14 (12·0)
Potentially contaminated	84 (70·6)	81 (70·4)	88 (75·2)
Contaminated	15 (12·6)	13 (11·3)	15 (12·8)
Depth subcutaneous fat (cm)±s.d.	2·0±1·01	2·1±1·2	2·0±1.1
Time taken to open (min)±s.d.	11·5±4·1	8·5±3·5	11·8±4·5
Range (min)	6–25	2–20	5–24

Values in parentheses are percentages

With a minimum follow-up of 1 year and maximum of 3 years no wound dehiscences or incisional hernias were observed in the 105 group A patients. In contrast, over the same period of follow-up 3 out of 104 incisional hernias were detected in group B (medial anterior sheath, lateral posterior sheath) and one wound dehiscence and 4 out of 109 incisional hernias in group C (lateral anterior sheath, medial posterior sheath). A highly significant difference exists between wound disruption/hernia rate in the lateral paramedian group and the combined results of the two variants ($\chi^2 = 10{\cdot}8$, $P < 0{\cdot}02$).

Discussion

The lateral paramedian incision has been criticised on two counts. Firstly, it undeniably takes longer to perform than conventional incisions, with a mean of 11·5 min in the present study. Comparison with our original report[1] indicates this time is only marginally reduced by familiarity (mean time 12·5 min in our original study). Present comparisons confirm this time is occupied largely by dissection of the anterior rectus sheath from the underlying muscle but it is our contention that this is more than compensated for by not having to resuture a wound dehiscence or incisional hernia. However, it is this extensive dissection which may account for the second criticism of the incision, namely the relatively high rate of wound infection (23 per cent) reported in our first study in which prophylactic antibiotics were not employed. Our current data would support the suggestion that this high infection rate is attributable to this component of the incision since there was a trend towards a higher rate of infection in those wounds in which a lateral anterior sheath dissection was performed. Despite this it would appear that the use of prophylactic antibiotics reduces infection rate of lateral paramedian incisions to a level comparable with that for other incisions when such prophylaxis is employed[5,6]. In addition, bearing in mind tissue reaction induced by catgut, with the consequent predisposition to sepsis which may ensue, further reduction in wound sepsis rates may occur if, as originally suggested by Ellis and Heddle[7], closure of the posterior sheath is demonstrated to be unnecessary. Results of extrapolation of this principle into the lateral paramedian incision have recently been reported by Professor Ellis' group with fascinating results[8]. Intrinsic strength of the lateral paramedian incision was confirmed even when the posterior sheath incision was not sutured. This is in accordance with the conclusion of the present study in which lateral incision of the posterior rectus sheath is found to be an important component contributing to the integrity of this incision. It would be of interest to know whether non-suture of the lateral incision in the posterior rectus sheath might also diminish the incidence of wound infection with this incision in the light of the fact that wound dehiscence and incisional hernia are not seen even when the lateral posterior sheath incision is not sutured.

This study was designed to determine whether or not technical modification of the lateral paramedian incision would overcome some of the objections to this incision but retain the advantages of the lateral paramedian incision with respect to wound dehiscence and hernia. Medial dissection of the anterior rectus sheath produced fewer wound infections than lateral dissection. In addition, it also greatly reduced time taken to perform the incision. Unfortunately this is at the cost of an increased wound hernia rate. Similarly, medial dissection of the posterior rectus sheath is also associated with significantly more wound complications. Thus, incision of the anterior or posterior sheath, in a plane more medial than that generally employed for the lateral paramedian incision, failed to confer any advantage other than reducing time taken to perform the incision. Such modifications carry an increased risk of wound dehiscence and incisional hernia. We conclude that lateral paramedian incision depends on lateral incision of both the anterior and posterior rectus sheath in order to provide the wide shutter mechanism which obviates risk of wound separation.

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Fascia closure after midline laparotomy: results of a randomized trial

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Four techniques to close the fascia after midline laparotomy were compared in a prospective randomized multicentre trial. The four techniques were: interrupted closure with polyglactin; continuous closure with polyglactin; continuous closure with polydioxanone-s, and continuous closure with nylon. The early postoperative results in 1491 patients revealed an incidence of wound infection of 8·6 per cent and of wound dehiscence of 2·3 per cent with no statistically significant differences between the four techniques. We reviewed 1156 patients after 1 year. Wound pain was present in 9·7 per cent of the patients, statistically significantly more in the group closed with nylon (16·7 per cent). Suture sinuses developed in 3·5 per cent of the patients, statistically significantly more frequently in the nylon group (7·7 per cent). The total number of incisional hernias detected 1 year postoperatively was high (15·2 per cent) (interrupted polyglactin 16·9 per cent, continuous polyglactin 20·6 per cent, continuous polydioxanone 13·2 per cent and continuous nylon 10·3 per cent). The difference between nylon and continuous polyglactin is statistically significant. The results of this trial indicate that although nylon has the lowest incidence of incisional hernia it also is associated with more wound pain and suture sinuses.

Keywords: Laparotomy, wound closure

There is an increasing tendency for the use of continuous sutures[1–4] to close midline abdominal incisions giving, theoretically at least, less tissue necrosis than interrupted sutures and being easier and less time consuming. Monofilament sutures are particularly advantageous when the continuous suture technique is used and the development of synthetic absorbable monofilament sutures was therefore of considerable interest.

Because the superiority of absorbable sutures over nonabsorbable sutures with the interrupted technique had been shown earlier[5] this study compares the interrupted and the continuous technique using synthetic absorbable multifilament and synthetic absorbable monofilament as well as synthetic nonabsorbable monofilament sutures.

The criteria used to assess the results were the occurrence of wound infection and wound dehiscence in the early postoperative period, and the occurrence of wound pain, suture sinuses and incisional hernia 1 year after operation.

Patients and methods

This multicentre randomized prospective trial was carried out in four surgical departments between March 1982 and May 1984. All patients having a laparotomy through a midline incision were included in the study, whether they had had a laparotomy before or not. The study therefore contained elective as well as acute operations, with all degrees of contamination as classified according to the National Research Council system[6]. The only patients excluded were those whose skin was not closed primarily, and those patients in whom the abdominal cavity was irrigated with antimicrobial agents or where local antibiotics had been used in the wound. The age, sex, height, weight, smoking habits, whether they suffered from chronic obstructive pulmonary disease or diabetes mellitus, the haemoglobin level, the total level of serum protein, previous use of corticosteroids, antibiotics and cytostatic drugs, previous radiotherapy, the presence of malignancy, diagnosis, nature and degree of contamination of the operation, length of the operation, whether it was an emergency or an elective operation, whether it was a relaparotomy, length and site of the incision and the thickness of the panniculus were recorded for all patients.

Randomization into each of the four groups of the study was carried out during the operation by the opening of an envelope. The technique used for closure of the abdominal wall was as follows. The peritoneum of the upper abdomen was either closed or left open, depending on the surgeon's preference. The peritoneum of the lower abdomen however, was always closed with a continuous suture with absorbable material of the surgeon's own choice. The subcutaneous tissues were not closed separately and the skin was closed with continuous nylon 3-0.

The fascia was closed by one of the following methods.

Group 1: interrupted multifilament polyglactin 910, no. 2 (Vicryl®-1)
Group 2: continuous multifilament polyglactin 910, no. 1 (Vicryl®-1) on atraumatic needle XLH
Group 3: continuous monofilament polydioxanone-s, no. 0 (PDS®) on atraumatic needle XLH
Group 4: continuous monofilament nylon no. 1 on atraumatic needle XLH

In the first 4 weeks after operation special attention was paid to the development of wound infection or wound dehiscence. A wound infection was defined as a purulent discharge from the wound spontaneously or after surgical drainage and when pathogenic micro-organisms were grown from wound fluids.

A wound dehiscence was considered to be present when a new operative closure of the fascia was necessary.

One year after the operation all patients who were still alive were again examined by the principal investigator (J.C.W.) and checked for wound pain, suture sinuses and incisional hernias.

An incisional hernia was considered to be present when a protruding swelling was noticed and a fascial defect was palpable in the wound during the examination of the patient in horizontal position lifting both legs, sitting up from the horizontal position, or coughing. A suture sinus was judged to exist when a micro-abscess or a chronic granulomatous inflammation resulted in a fistulous tract which could only be cured when the relevant suture or knot was removed.

Statistical methods

All data were analysed by computer using the χ^2 test (significance $P<0\cdot05$) followed by a two by two test of percentages with reduced reliability level (method of Bonferroni)[7].

Results

A total of 1539 patients were randomized, 48 subsequently were withdrawn either because they died ($n=21$) or underwent a relaparotomy because of unrelated disease ($n=9$) within 4 weeks of the primary procedure or because administrative mistakes were made ($n=18$). Therefore the early results in 1491 patients could be analysed, with only a small amount of missing data.

These 1491 patients were equally divided over the four trial groups which showed no statistically significant differences as far as age, sex, risk factors, type of operation, degree of contamination, malignancy, use of corticosteroids or use of antibiotics were concerned (*Table 1*).

Table 1 *Comparability of trial groups*

	Group 1 ($n=365$)	Group 2 ($n=379$)	Group 3 ($n=370$)	Group 4 ($n=377$)
Patients				
Male (%)	59·8	56·7	59·0	57·4
Female (%)	40·2	43·3	41·0	42·6
Age distribution (%)				
<45 years	26·8	27·9	22·8	28·2
45–59 years	26·0	22·4	23·9	26·9
60–69 years	19·4	23·4	24·9	23·2
⩾70 years	27·9	26·3	28·4	21·7
Risk factors (%)				
Pulmonary disease	11·2	13·1	12·5	11·4
Diabetes	6·1	6·8	5·6	5·8
Obesity	28·3	28·1	30·4	28·2
Type of operation (%)				
Large intestine	21·8	22·3	19·7	19·6
Small intestine	4·5	5·5	5·4	5·0
Biliary tract	14·6	16·8	19·7	19·6
Stomach	19·7	12·1	13·8	15·6
Vascular	9·8	14·7	12·7	12·4
Various	29·5	28·6	28·6	27·8
Degree of contamination (%)				
NRC I	48·1	47·5	46·3	49·3
NRC II	39·2	39·4	38·6	36·7
NRC III	5·6	7·8	8·8	7·9
NRC IV	7·1	5·2	6·4	6·0
Malignancy (%)	35·4	26·8	26·1	25·3
Steroid therapy (%)				
Chronic	1·6	4·2	3·7	3·7
Acute	2·9	1·8	1·3	1·8
Emergency operation (%)	20·0	21·0	21·0	20·8
Antibiotics (%)				
Prophylactic	60·1	67·2	57·3	60·8
Therapeutic	4·8	5·2	7·7	7·0

There were no statistically significant differences between factors

Early complications (Table 2)

A wound infection was seen in 8·6 per cent ($n=128$) of the patients. There were no statistically significant differences between the four trial groups.

A wound dehiscence was noted in 35 patients (2·3 per cent), the differences between the trial groups not being statistically significant. In only 9 of these 35 patients the cause of dehiscence was given by the reoperating surgeon (6 fascial tears, 3 a loosened knot).

In NRC I (clean) operations a dehiscence was noted in 1·7 per cent, in NRC II (clean-contaminated) in 1·7 per cent, in NRC III (contaminated) in 4·5 per cent and in NRC IV (dirty) in 8·8 per cent of the cases. The differences between groups NRC I and NRC II and NRC IV are statistically significant ($P<0\cdot009$). The percentages of wound dehiscence in the four participating centres were 2·5, 0·8, 4·0 and 2·9 respectively; the difference between the lowest and the highest percentage being statistically significant ($P<0\cdot009$).

Late postoperative complications (Table 3)

One year after operation 1206 patients were available for follow up, 334 having died or having had a relaparotomy for unrelated disease. Of these 1206 patients only 40 (2·7 per cent) could not be contacted leaving 1156 for their one year re-examination giving a complete follow up in 97·3 per cent of the original group.

Pain in the wound was complained of by 112 patients (9·7 per cent) nearly half of them having had their fascia closed with continuous nylon. Statistically there was a significant difference ($P<0\cdot009$) in comparison with the other three groups. Of the patients who had a wound infection in the early postoperative period 21·7 per cent ($n=20$) later experienced wound pain in contrast with only 8·5 per cent ($n=91$) in the patients without wound infection; a statistically significant difference ($P<0\cdot05$).

During the one year postoperative follow-up period a suture sinus developed in 41 patients (3·5 per-cent), with a significantly higher number in the group of patients with a continuous nylon closure ($P<0\cdot009$) than in the group having a polyglactin closure.

There was also a clear correlation between the development of a suture sinus and earlier wound infection. Of the patients with a wound infection 15·2 per cent ($n=14$) later developed a

Table 2 *Early postoperative complications*

	Group 1 (interrupted polyglactin) ($n=365$)	Group 2 (continuous polyglactin) ($n=379$)	Group 3 (continuous polydioxanone) ($n=370$)	Group 4 (continuous nylon) ($n=377$)	P
Wound infection n (%)	24 (6·6)	34 (9·0)	43 (11·6)	27 (7·2)	n.s.
Wound dehiscence n (%)	8 (2·2)	6 (1·6)	13 (3·5)	8 (2·1)	n.s.

Table 3 *Late postoperative complications*

	Group 1 (interrupted polyglactin) ($n=286$)	Group 2 (continuous polyglactin) ($n=290$)	Group 3 (continuous polydioxanone) ($n=281$)	Group 4 (continuous nylon) ($n=299$)	P
Wound pain n (%)	14 (4·9)	25 (8·6)	23 (8·2)	50 (16·7)*	<0·009
Suture sinus n (%)	3 (1·0)*	4 (1·4)†	11 (3·9)	23 (7·7)*†	<0·009
Incisional hernia n (%)	48 (16·7)	60 (20·6)*	37 (13·2)	31 (10·4)*	<0·009

*† Significant difference, $P<0\cdot009$

suture sinus in contrast with 2·4 per cent ($n=27$) of the patients without wound infection ($P<0.05$).

An incisional hernia had developed within 1 year in 15·2 per cent of the patients ($n=176$). The number of incisional hernias was the highest in the group closed with continuous polyglactin (20·6 per cent) and lowest in the group closed with continuous nylon (10·3 per cent). The difference between these two groups was statistically significant ($P<0.009$). A clear correlation between a postoperative wound infection and the development of an incisional hernia was noted. No less than 43·5 per cent ($n=40$) of the patients with a wound infection developed an incisional hernia in contrast to only 12·7 per cent ($n=135$) of the patients without wound infection, the difference being statistically significant ($P<0.05$). However, in the group of patients having a wound infection the kind of fascial closure did not have an influence on the development of an incisional hernia.

No correlation was found between pulmonary disease, male sex, postoperative chest infection, diabetes mellitus, anaemia and hypoproteinemia and the development of an incisional hernia.

A relationship existed between wound infection and obesity and the degree of contamination. The type of fascial closure was of no importance in this context.

Discussion

Experimental research[8] has shown that one year after a laparotomy the abdominal fascia retains only 70 per cent of its original strength which means that the fascia preferably needs a long lasting, supporting suture. Synthetic absorbable sutures such as polyglycolic acid and polyglactin which have become available in the last decade, do have the advantage that they disappear in time but, because they are fully absorbed after 70 days and have no strength left after 30 days, they are in theory not ideal for closure of the abdominal fascia.

The newest development in synthetic absorbable sutures, polydioxanone-s, is only absorbed after 180 days and retains 70 per cent of its strength after three weeks[9]. Polydioxanone-s is a monofilament suture and therefore also has the advantages of other monofilament sutures such as nylon and polypropylene. Primarily they offer a smooth surface which slides easily through the tissues, giving a better spreading of tension over the wound which reduces the chance of tissue necrosis[10]. Secondly the adherence of bacteria to a monofilament thread is considerably less than that to multifilament sutures such as polyglactin[11].

The benefits of the continuous closure method have been shown repeatedly in recent years[1–4]. It was the objective of the present study to compare the various synthetic absorbable sutures available today as well as the interrupted and continuous method of closure. Monofilament nylon was included because it can be regarded as 'the gold standard' in continuous closure[12]. The results of our study show that the kind of suture material used does not influence the development of early postoperative complications such as wound infection and wound dehiscence.

The incidence of wound dehiscence was rather high (2·3 per cent) in comparison with an earlier study from one of the participating hospitals[5]. The fact that the present study was a multicentre trial with a large number of surgeons of all grades of experience and also the relatively small number of contaminated and dirty operations in the earlier study may explain this difference.

Figures of 1·5–3 per cent for wound dehiscence are found in the literature[13,14].

We did not find a statistically significant difference in the development of wound dehiscence between the continuous and the interrupted technique either. This finding confirmed the results of a recently published French trial[14] in which polyglycolic acid and polyglactin were used as suture materials. These investigators found an incidence of 1·6 per cent in the continuous group and 2 per cent in the interrupted group.

In contrast with the early postoperative findings the long term results of our study showed clear differences between the various groups. The total number of incisional hernias (15·2 per cent of the patients) was strikingly high comparing unfavourably with the 1–10 per cent reported in the literature[15,16]. The lowest incidence was found in the patients closed with nylon (10·3 per cent), continuous polydioxanone being the second best (13·2 per cent), polyglactin giving 16·9 per cent incisional hernias when it was used interruptedly and 20·5 per cent when used continuously. One explanation for the high incidence of incisional hernias in this study could be the careful way the patients were checked one year after surgery with a complete follow-up in 97·3 per cent of the patients. The literature shows that 52 per cent of incisional hernias appear within 6 months after operation, 68 per cent within 1 year and 79 per cent within 2 years[17]. A great number of patients had only a small hernia, the patient himself not being aware of its existence and having no spontaneous complaints.

This study again confirmed the fact that the development of an incisional hernia is very frequently (40·3 per cent) preceded by a postoperative wound infection indicating that for practical purposes the prevention of wound infection is more important in the avoidance of incisional hernias than the kind of suture material or the type of closure used.

One of the disadvantages of the use of nonabsorbable suture material was seen also in this study i.e. the high percentage of patients with wound pain (16·7 per cent) and suture sinuses (7·7 per cent). But, surprising as it may seem, the use of absorbable material cannot completely prevent the development of suture sinuses (2 per cent) confirming the results of an earlier study (1·2 per cent)[5].

In conclusion the use of continuous nylon gave the lowest incidence of incisional hernia at 1 year follow-up examination. Nylon, however, was associated with significantly more wound pain and suture sinuses, disadvantages which polydioxanone and polyglactin did not have. When one uses the continuous closure technique, polydioxanone as the suture material seems to be a good choice, while polyglactin gives comparable results when the interrupted technique is preferred.

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Pumping device for re-infusion excretions derived from a proximal jejunostomy or high output fistula

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Patients with a jejunostomy or high output enteric fistula are liable to suffer from electrolyte disturbances, fluid balance problems, trace element deficiencies, disturbances in the enterohepatic circulation probably responsible for hepatic dysfunction, and loss of valuable visceral proteins. In spite of the availability of total parenteral nutrition (TPN) the management of these small bowel fistulae or proximal jejunostomies is difficult. If patients also have a distal jejunostomy or ileostomy it is often possible to prevent most of the above problems by collecting and re-infusing the output of the proximal stoma into the distal stoma. The dumping syndrome may occur, however, when the fluid is not administered by constant infusion. A safe and simple method has been developed for continuous infusion of excretions derived from proximal jejunostomy or high output fistula into a distal enterostomy.

Technique

A collection bag is applied to the proximal enterostomy. The bag is connected to an infusion set which is then connected to a urinary bladder catheter which is inserted into the distal stoma (*Figure 1*). A roller pump (R/Fenwol TR400, Travenol) is used to transfer the fluid, and its pumping rate can easily be adjusted to the fluid level in the collection bag. If a turbid solution is excreted the fluid is filtered and then re-infused using a roller pump or an IVAC IV fluid pump. Excretions, however, have to be collected every 4 h to avoid severe bacterial contamination.

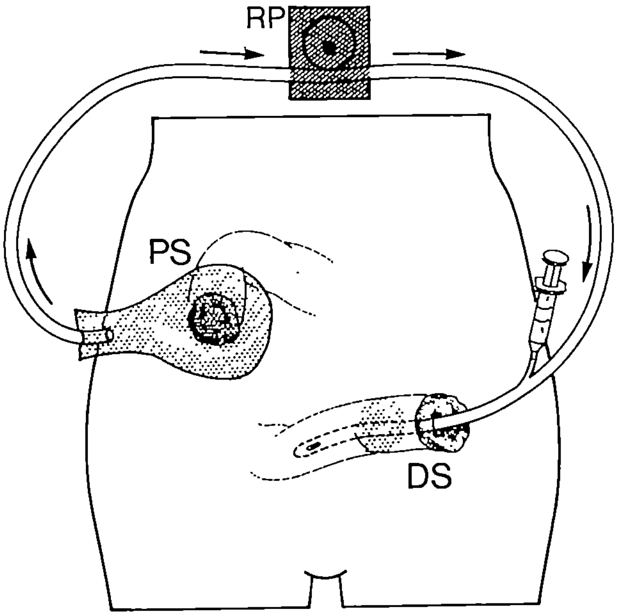

Figure 1 *Outline of pumping device with a collection bag around the proximal stoma (PS). The roller pump (RP) is adapted to an infusion set and to a catheter placed in the distal stoma (DS)*

This pumping device has been used in six patients. One patient had a proximal and distal jejunostomy and a proximal and distal ileostomy and two separate pumping devices were applied. Excretions were replaced for a mean period of 21 days. Complications were not observed. In one patient the infusion was stopped during a period of sepsis unrelated to replacement of the excretion solution. Patients could be mobilized with the pumping device *in situ* while recovering, awaiting a definitive re-anastomosing procedure. Liver function tests were abnormal in all patients before infusion, probably related to intestinal bacterial overgrowth. Serum bilirubin levels were increased to six times normal values, alkaline phosphatase up to 500 units/l (normal < 120 units/l) and SGOT (serum glutamic oxalo-acetic transaminase) and SGPT (serum glutamic pyruvic transaminase) were increased slightly up to four times normal values. The liver function test normalized or improved after replacement of the excretions in spite of continued TPN.

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Natural history and surgical management of radiation enteritis

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Radiation enteritis is an increasing problem. The effect of ionizing radiation is due to a direct effect on proliferating cells and due to a progressive obliterative vasculitis. Predisposing factors include the dose of radiation, combination with chemotherapy, previous operations and vascular disease. Management is related to the stage of disease at presentation, and tailored to the clinical problem. Surgical management must take into account the poor healing associated with irradiated intestine.

Keywords: Radiation enteritis

Roentgen's discovery in 1895 of 'a new kind of ray' heralded a new and effective form of treatment for many malignant diseases. Within 2 years of that discovery, however, the acute gastrointestinal effects of abdominopelvic radiotherapy had been reported[1]. Before the end of the First World War cases of radiation-induced rectal strictures and fistulae had already been published[2].

It has been suggested that half of all patients with malignant disease will at some time undergo radiotherapy, many with the hope of a permanent cure[3]. However, radiation enteritis, in patients undergoing abdominopelvic radiotherapy, can lead to disability and ultimately death, long after the original malignancy has been controlled.

The incidence of radiation enteritis appears to be increasing. In our department, of 70 patients presenting between 1958 and 1984, more than half did so in the last 10 years of the study[4]. Others have noted a similar progressive increase in recent years[5]. The combination of internal and external treatment, which has been shown to increase the likelihood of radiation damage, has become increasingly popular recently, and the newer technique of 'afterloading' may be among the factors responsible for this increase. Therefore, the disease is becoming increasingly important and its surgical implications will be discussed.

Intestinal tolerance to radiotherapy

Doses of radiation producing clinical damage in up to 5 per cent or up to 50 per cent of patients within 5 years are termed TD5/5 and TD50/5 respectively. The range is 6000–7500 cGy for oesophagus, 4500–5000 cGy for stomach, 4500–6500 cGy for small bowel and colon and 5500–8000 cGy for rectum[6]. These doses are very close to the therapeutic dosages required to control many of the commoner tumours. For example, the average doses given for cervical or endometrial cancer, ovarian cancer and bladder cancer are 4000–8000 cGy, 4000–5500 cGy and 4000–6000 cGy respectively. Not surprisingly, the greater the dosage given the higher the subsequent risk of radiation damage. Such damage is particularly common when intracavitary treatment is combined with external beam therapy.

Pathophysiology

The effect of ionizing radiation on the gut wall is twofold. There is a direct effect[7] and then an indirect effect due to progressive obliterative vasculitis[8]. These effects which are summarized below are described in detail elsewhere[9,10]. The relative importance of the rate at which the radiation is given, the total dose of radiation and the total volume of tissue irradiated in the production of acute, intermediate and late effects is shown in *Table 1*.

The acute effects consist principally of depletion of actively proliferating cells in an otherwise stable cell-renewal system. Damage occurs when depletion exceeds repletion. Histological abnormalities can be seen within hours of the administration of therapeutic doses of radiation. Small bowel mitoses are reduced in number and villi become shortened with a reduction in total absorptive area. A cellular infiltrate, predominantly consisting of leucocytes, occurs in the next 2–4 weeks with crypt abscess formation. Complete histological recovery is usual within 6 months of completion of the treatment. During this acute phase there is malabsorption and impaired metabolism of bile salts, fat, carbohydrates, protein and vitamin B_{12}.

The late sequelae of radiation enteritis are apparent macroscopically as the gut becomes thickened with areas of telangiectasia. Mucosal ulceration is common and may go on to involve the whole gut wall. Extension of this process leads to perforation, fistulae or the formation of local abscesses, while resolution results in strictures. The main histological features of

Table 1 *Relationship between administration of radiotherapy and production of acute, intermediate and late effects*

	Acute	Intermediate	Late
Determinants			
Dose rate	+		
Time:dose characteristics	+	+	
Volume irradiated	+	+	+
Total dose		+	+
Tissue injured	Actively proliferating cells Depletion > repletion	Endothelium and connective tissue	

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late damage include obliterative endarteritis, submucosal fibrosis and oedema, lymphatic ectasia and abnormal (star-shaped) fibroblasts. In a study of the microradiography of resected specimens, Carr *et al.*[11] demonstrated reduced and abnormal vascularity in irradiated, compared with non-irradiated colons. Furthermore, they showed regions of completely avascular gut wall corresponding to areas of infarction.

Predisposing factors

The following factors predispose to radiation injury although it should be stressed that some patients develop evidence of damage in the absence of any identified predisposing factor.

Excessive radiotherapy

Early reports of patients with radiation-damaged gut suggested that there were large numbers of patients in whom the doses of radiotherapy were excessive by today's standards. This may still be a factor when large or recurrent tumours are being treated, and the risk and benefit of the treatment need to be carefully balanced.

Combined chemotherapy

When chemotherapy is given, with or immediately after radiotherapy, the effect of the radiotherapy has been shown, experimentally and clinically, to be enhanced. Unfortunately, the effect on surrounding, normal tissues is also increased. Many drugs have been implicated, including actinomycin D, 5-fluorouracil, methotrexate and Adriamycin[12,13]

The patient's build

Thin patients, women, and the elderly all have an increased amount of small intestine in the pelvis[14]. Accordingly these people have a higher risk of sustaining small intestinal damage when exposed to pelvic radiotherapy.

Factors in patient's past history

Previous abdominopelvic operations. There is increasing evidence to suggest that previous operations predispose to late radiation damage. Loiudice *et al.*[15] studied retrospectively a group of patients which had undergone radiotherapy. The group was well matched except that half had radiation enteritis and half did not. Those who developed bowel damage were significantly more likely to have had previous operations. It is usually stated that this effect is due to the production of intra-abdominal adhesions which fix lengths of gut, thereby exposing the same lengths of bowel to excessive radiation. In a radiological study of gut mobility, Green[16] found an increased likelihood of gut being relatively immobile or fixed in the presence of previous operations. However, the ability of gut to move when filled with contrast medium does not necessarily imply that such gut moves freely around the abdomen during normal activities.

Vascular occlusion. Conditions which cause vascular occlusion might reasonably be expected to predispose towards radiation injury. DeCosse *et al.*[17] demonstrated a significant association between hypertension, diabetes and cardiovascular disease at the time of radiotherapy and the subsequent development of radiation enteritis.

Prevention of radiation enteritis

Stewart and Gibbs[18] described what they called a 'logical (radio) therapeutic approach' based on the predictability of complications. They suggested that injury could be minimized by precise localization of the tumour and its likely field of spread, precise direction of the radiation beam, treatment planning computers and dose adjustment, depending on previously defined risk factors and whether the aim of the treatment was palliative or curative. Hyperfractionated radiotherapy may also prove useful in reducing the incidence of late complications.

Radioprotective agents

Substances given prophylactically with therapy have been studied, but their precise role has yet to be fully evaluated. In a small, prospective study. Bounous *et al.*[19] demonstrated a reduction in acute gastrointestinal symptoms in those patients randomized to receive an elemental diet during treatment. The mechanism of this action is not clear, but elemental diets have been shown to reduce bile salt secretion, the latter having been implicated in the production of radiation enteritis. In a series of largely retrospective analyses, alkoxyglycerols were protective when given immediately before, during and immediately after radiotherapy[20].

Exclusion of gut from radiation field

Radiological mapping of small bowel has shown it to be at risk in about 60 per cent of patients undergoing abdominopelvic radiotherapy[14,16]. Use of the Trendelenburg position, or distending the bladder with water, pushes the ileum out of the radiation field. Using these techniques, allied with reduction of total dose or field size as required, Green *et al.*[14] found no cases of small bowel damage after an average follow-up of 3 years. This was achieved with little compromise of tumour control.

Other techniques employed to keep the small bowel out of the pelvis have included the introduction of omental pedicles, silastic implants or mesh slings into the pelvis, and suturing the bladder to the sacrum[21,22]. Others have emphasized the importance of closure of the pelvic peritoneum after abdominoperineal excision of the rectum, particularly as radiotherapy is becoming more acceptable as a treatment for late local recurrence of rectal carcinoma.

Natural history

Acute effects

During a course of abdominal or pelvic radiotherapy most patients experience diarrhoea, nausea, vomiting, abdominal pain or tenesmus. These symptoms usually subside spontaneously within a few weeks of completion of the treatment course[10] and most of the patients have no further trouble. There is some evidence to suggest that patients who experience the worst acute reactions are at greater risk of developing later gastrointestinal complications[23]. However, even patients who experience no acute effects are still at risk of developing later complications.

Subclinical effects

The gut can be chronically damaged while showing no manifestation of injury. Newman *et al.*[24] investigated 17 consecutive patients attending a radiotherapy follow-up clinic, none of whom complained of any gastrointestinal symptoms. They found that 12 had a permanent alteration in their bowel habit and 16 had evidence of malabsorption. This clearly has important surgical implications in that the resection of even a small length of bowel may be sufficient to produce overt malabsorption.

There are hazards of operating on patients who have had radiotherapy even though the irradiated bowel remains asymptomatic. We described three patients who had laparotomies at varying intervals after pelvic radiotherapy. In each case the gut appeared normal, and in each a spontaneous perforation of the gut became apparent in the immediate postoperative period[25]. The mechanism of the injuries sustained in these cases is not clear.

Late effects

The precise incidence of late radiation effects on the bowel after abdominopelvic radiotherapy is unknown. The usual accepted figure is between 2 and 5 per cent[5] though higher rates have been reported. The latent period between completion of the course of radiotherapy and the subsequent development of radiation bowel damage is usually 6–24 months. However, it is clear that radiation enteritis can become apparent many years after the original treatment and should always be considered when a patient who has had radiotherapy presents with abdominal problems. Recurrence of the original malignancy should not be assumed without excluding radiation damage.

Apart from malabsorption, which is often subclinical, proctosigmoiditis appears to be the commonest form of disease, and comprised nearly three-quarters of the cases in one series[26]. Gilinsky *et al.*[27], reviewing 88 patients with radiation-induced proctosigmoiditis, found that those who had not required blood transfusions, and who had little or no bowel disturbance or pain, had a high rate of spontaneous remission, and usually did not need an operation. By contrast, those patients whose bleeding was sufficiently severe to require transfusion, or in whom there was a significant bowel disturbance, rarely underwent spontaneous remission and were more likely to need operation. The radiation-induced mortality was significantly higher in the latter group of patients.

Radiation enteritis is a progressive disease. In our own series, of 51 patients, only 24 (47 per cent) remained symptom-free at a median follow-up of 1 year[28]. Of the remainder, 20 developed new radiation-related gastrointestinal problems. None of the patients first presenting with bleeding developed new problems, compared with 33 per cent of those with stricture and 89 per cent of those with perforation or fistula, who went on to manifest new lesions. Patients first presenting with fistulae also appear to be at increased risk of having synchronous radiation lesions at the time of presentation[29] and of dying, within a relatively short time, of recurrent malignant disease[30].

Development of radiation-induced malignancy

It has been shown experimentally that 47 per cent of rats exposed to 4500 rads will develop colonic adenocarcinomas within 7·5 months[31]. We examined colonic resection specimens from 26 patients with radiation-induced colitis and found a significant increase in the number with dysplasia and mucin abnormalities (representing pre-malignant field changes) compared with controls[32]. The relative risk of developing colonic carcinoma after radiotherapy has been calculated as being 2–3·6[33]. This allows for the fact that a tumour arising in an irradiated field may be an incidental finding and that women with gynaecological malignancy are at increased risk of developing colonic tumours[34]. Black and Ackerman[35] defined a colonic cancer as being radiation-induced if there was severe associated radiation damage and if more than 10 years had elapsed since completion of the therapy.

Associated radiation damage

The urinary tract is frequently injured in the presence of bowel damage. DeCosse *et al.*[17] described 55 cases of urinary tract injury in 100 patients with radiation enteritis. In 44 the injury was to the bladder and in 16 cases the symptoms were described as 'severe'. Schofield *et al.*[36] reported that several of their patients developed urinary symptoms following successful management of the gastrointestinal problem.

Other injuries described include radiation myelitis, osteitis pubis, pathological fractures and atheromatous changes in blood vessels in the radiation field.

Cause of death

Most deaths in these patients are due either to recurrent disease or to the effects of radiation on the gut. The overall 5 year survival of our patients was 42 per cent. Radiation enteritis was responsible, either directly or indirectly, for the death of 23 of 37 patients who died. Nine of these patients died with no evidence of their original tumour[28]. Many of these deaths would now be regarded as being avoidable with improvements in the operative management of these patients.

Management

Conservative

Enterocolitis. For abdominal pain, diarrhoea and vomiting, occurring during radiotherapy, a 10 per cent reduction in the daily dose of radiation may be enough to reduce abdominal symptoms without compromising tumour control[10]. Should this fail, symptomatic relief with antispasmodics, anticholinergics or opiates has been described.

Acute enterocolitis may be, at least in part, prostaglandin mediated. In a small prospective trial, Mennie *et al.*[37] found that aspirin, given as buffered acetyl salicylate, a prostaglandin-E synthesis inhibitor, caused significant decrease in diarrhoea, pain and flatulence compared with placebo. Cholestyramine, which binds bile salts, has also been found to be effective for diarrhoea[38].

Various dietary manipulations have been recommended. In the acute situation these have included diets low in milk, fat and lactose[19]. A recent study evaluating total parenteral nutrition for patients with predominantly chronic small bowel problems found that it was significantly better at improving clinical, immunological and radiological parameters than a low residue diet. The addition of methylprednisolone appeared to enhance the effect of the total parenteral nutrition[39].

Salazopyrin and oral prednisolone have both been used empirically, occasionally with good results.

Proctitis. In the acute phase hydrophilic stool softeners may help to control mucous diarrhoea, while Sitz baths and perineal compresses have been used in an attempt to ease tenesmus if simple analgesics fail. Steroid retention enemas also appear useful in both acute and chronic radiation proctitis. In a recent study, Jacobs *et al.*[40] found that the administration of oral or rectal Salazopyrin alleviated the symptoms of acute and chronic radiation proctitis in 37 of 40 patients so treated. Similar results have been claimed when the inflammation involves the rectum and sigmoid colon[41].

Surgical

Before definitive treatment is considered it is important that the extent of both the original malignancy and the radiation damage should be established and any sepsis, malnutrition or biochemical abnormalities be corrected.

Resection and primary anastomosis. Removal of the radiation-induced lesion followed by immediate anastomosis has been widely practised. However, by the late 1970s it became apparent that, owing to the poor healing capabilities of irradiated bowel, there was a high rate of anastomotic leakage and operative mortality following such procedures[42–47]. Furthermore, repeated anastomotic breakdown in small bowel was described[48].

Ideally, the two ends of the bowel anastomosed should be clear of disease. However, although macroscopically diseased bowel may be recognized easily, it is often impossible to differentiate normal gut from that which is damaged microscopically. Frozen section is not helpful in this circumstance.

'Wide resection' is clearly the ideal and is frequently advocated. But, how wide should wide resection be? Most authors make no attempt to define this. Schofield *et al.*[36] suggest that in ileal resection at least 50 cm of gut should be removed. The problem of anastomotic leakage following primary anastomosis can be largely overcome by using gut for one end of the anastomosis which is taken from outside the original radiation field. For example, in patients who have had pelvic radiotherapy the ascending, transverse and descending colons are usually free of injury. Since 1977 we have followed terminal ileal resection by an ileo-transverse anastomosis and

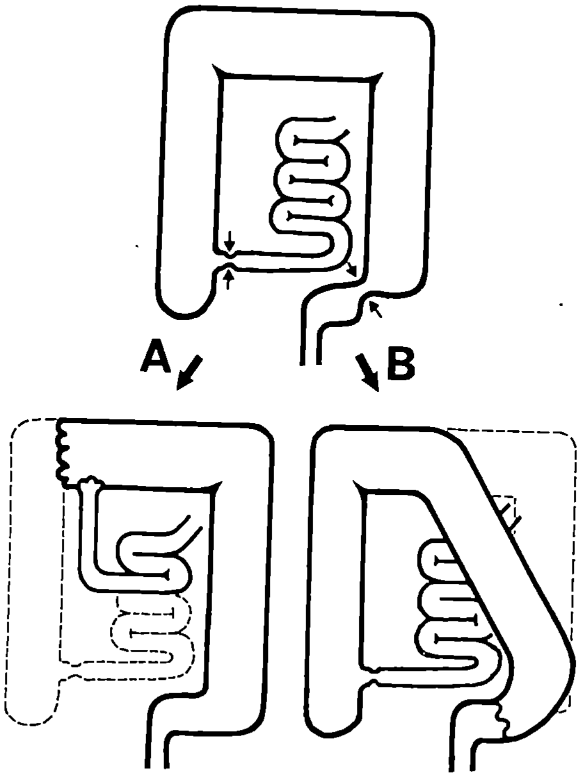

Figure 1 *Terminal ileal lesions treated by right hemicolectomy and ileo-transverse anastomosis (A) and rectosigmoid lesions treated by left hemicolectomy bringing the splenic flexure down for anastomosis (B). Reprinted from Reference 4, with permission of the editor of* Surgery

rectosigmoid resection by mobilization of the splenic flexure to bring it down for anatomosis (*Figure 1*). Using these techniques there was only one (radiological and non-clinical) leak in 14 anastomoses with no patients dying. This was a significant improvement on our results up to 1977, where 14 of 27 anastomoses leaked, 10 of the 24 patients dying[4]. Using similar techniques, Marks and Mohiudden[49] described no leaks in intraperitoneal anastomoses and only four in fifty-two extraperitoneal rectal anastomoses. Similarly, Bricker *et al.*[50] achieved good functional results in 18 of 21 patients with rectal stricture or fistula. In this series the authors emphasized that resection or mobilization of the damaged rectum was not necessary and that normal colon should be brought down and anastomosed to the anterior wall of the rectal ampulla[50,51].

In the face of extensive distal disease, where even the anal canal may be damaged, any attempt at restorative resection can be dangerous. Under such circumstances, an abdominoperineal excision may be all that is possible. Of 47 patients with colonic damage in the series described by Schofield *et al.*[36], no fewer than 15 required an abdominoperineal excision of rectum. All of these patients made a satisfactory recovery, and about half were well at the time of follow-up; the remainder had recurrent disease and/or severe urinary tract symptoms.

Resection followed by an ileostomy or colostomy and mucous fistula may be appropriate in certain circumstances, particularly if there is peritoneal contamination from perforation. If subsequent histology confirms the presence of radiation damage at the lines of resection, it is clear that further resection is required before anastomosis. However, even if the resection margins are apparently healthy, a safe subsequent anastomosis cannot necessarily be guaranteed since the disease may have progressed since the first operation.

Occasionally, very high small bowel lesions need to be resected. Clearly, in these circumstances an ileo-transverse anastomosis, as outlined earlier, would be inappropriate. There are no hard data on the safest way to manage such cases; however, we have followed resection by a side-to-side anastomosis using a GIA stapler with good results in a small number of cases. A long intestinal tube placed across such an anastomosis has been advocated by some authors[45].

In 1976 Palmer and Bush[52] described 31 anterior resections performed on irradiated bowel with only two anastomosis leaks. The only apparent difference in their technique compared with that of others was that 'a pedicle of omentum was sutured around the anastomosis in all patients'. The importance of having non-irradiated tissue surrounding an anastomosis was recently shown experimentally by Ormiston[53]. In rats, the suture line dehiscence rate was higher if both gut and fatty appendages of the epididymis (equivalent to the omentum) were irradiated than if gut alone was irradiated. This may partially explain why using transverse colon for one end of an anastomosis, as described earlier, is so effective, as the anastomosis can be surrounded by non-irradiated omentum.

Bypass, exclusion procedures and colostomies. In 1976 Swan *et al.*[54] selected 199 patients from the English literature who had been treated by resection and anastomosis or bypass procedures. They found that 36 per cent of patients having had resection and anastomosis experienced anastomotic leakage, with an operative mortality of 21 per cent. By contrast, where bypass procedures had been performed, the leakage rate was 6 per cent with a 10 per cent mortality. They provided similar results from a series of 45 patients of their own. Their conclusion was that bypass procedures were the operation of choice in patients with radiation enteritis. Unfortunately bypass procedures, including defunctioning colostomy for rectal lesions, suffer from the drawback that diseased bowel is left *in situ* and may go on to cause further trouble. In our series, of 22 patients so treated, rectal bleeding continued in 4 and bypassed gut perforated or fistulated in 3 others[4].

Simple colostomy may be all that is feasible in patients who are unfit for more extensive surgery or in whom a frozen pelvis precludes any other option. In these circumstances, it is once more important to raise the colostomy in bowel which is likely to have been outside the original radiation field. DeCosse *et al.*[17] found that almost half of their colostomies performed in sigmoid colon subsequently required re-fashioning for gangrene, stenosis or haemorrhage. No such problems arose when colostomies were made in transverse or descending colon. If there is any likelihood that reconstructive surgery may be attempted later, then the colostomy should be sited in the right transverse colon so that ultimately the splenic flexure can be mobilized for anastomosis as described earlier.

Fistulae. These may be particularly difficult to manage and deserve special mention. The association between fistulae and synchronous radiation-induced lesions has already been mentioned. If there is any suggestion of subacute bowel obstruction or urinary symptoms along with the fistula, then appropriate investigations should be performed, so that the operative procedure(s) can be planned carefully in advance. Furthermore, malnutrition may complicate high small bowel fistulae and ascending urinary tract infection and renal failure may be associated with entero-urinary fistulae.

A proximal defunctioning colostomy is likely to be an important preliminary step in colorectal fistulae. The delay between creating the colostomy and the definitive operation will vary, depending on such factors as whether the fistula has developed as part of an acute radiation reaction. In these circumstances, a prolonged delay may be required to allow full resolution of the inflammation. More usually, the fistula develops later in the course of the disease and in carefully selected patients, who have no acute reaction or acute inflammation, a combined colostomy and reconstruction may be appropriate[50].

Direct local repair of fistulae is likely to fail, firstly owing to the rigidity of tissue, and secondly because irradiated tissue heals so poorly. Clearly, non-irradiated tissue should be brought into the area for use in the repair. In the case of rectovaginal fistulae, the interposition of muscle or omentum may be sufficient to allow satisfactory healing. Of 21 rectovaginal or vesicovaginal radiation fistulae, repaired using a pedicled gracilis flap, satisfactory healing and normal function were obtained in 16[55]. Anterior resection of rectovaginal fistulae is likely to be precluded due to the low level of the fistula. However, the colo-anal pull-through anastomosis may be of value. In this procedure, the mucosa is stripped from the lower rectum and the mobilized descending colon is pulled through the muscular tube to the anal region, the fistula being left untouched[56]. The obvious potential disadvantage of this operation is that the remaining rectal muscular tube may go on to stricture later. However, using this technique Cooke and DeMoor[57] achieved good results in 28 patients having rectovaginal fistulae. There were two primary failures and two other anastomotic leaks, but the remainder all healed satisfactorily, and at a follow-up of 1 year 75 per cent achieved full continence. Further follow-up confirmed the value of this technique in a larger group of patients[58]. This method has also been used successfully for treating rectal bleeding and stricture[59].

For small bowel fistulae resection may not always be possible; the bowel may, for example, be matted down in a frozen pelvis. A bypass procedure may be all that is possible and in these circumstances Piver and Lele[60] found that bypass combined with isolation of the fistula was safer than bypass alone.

In conclusion, although radiation enteritis is perhaps no longer the 'enigma' described by Morgenstern *et al.*[45], its progressive nature and the poor healing capacity of damaged gut will continue to tax the skill and ingenuity of surgeons for many years to come. Our greater knowledge of the natural history of the disease, together with improved results of surgical treatment should allow us, if not to cure, then at least to palliate successfully most of those patients whom we treat.

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Role of Enterobius vermicularis in the aetiology of appendicitis

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An evaluation was made of the histological material obtained from all 1529 appendices removed during the last 5 years at Southmead Hospital, Bristol, in order to elucidate possible relationships between the incidence of Enterobius vermicularis *and the origin of inflammation in the appendix. In total, 1419 appendices were removed as cases of clinical appendicitis and 110 in the course of another surgical procedure.* E. vermicularis *was identified in 2·7 per cent of patients with clinical appendicitis and was most commonly seen in appendices with either chronic inflammation or where the appendix was histologically normal.* E. vermicularis *was rarely associated with histological changes of acute appendicitis. No cases of* E. vermicularis *infestation occurred in appendices removed during the course of other surgical procedures. The results suggest that, although* E. vermicularis *may have a causal role in appendicular pain and chronic inflammation, it is rarely related to acute appendicitis.*

Keywords: *Enterobius vermicularis*, appendicitis, inflammatory reactions

Infestation of man with *Enterobius vermicularis* (pinworm, threadworm, seatworm, oxyuriasis) has been recognized for thousands of years[1] and the presence of the parasite in the appendix was first reported by Fabrius in 1634.

The mature worm lives and reproduces in the terminal ileum, caecum, vermiform appendix and the proximal part of the ascending colon. After fertilization, the male worm dies while the female migrates to the anal canal where the laying of eggs takes place. This process, occurring especially at night, causes intolerable itching which leads to further contamination of the hands and re-cycling of the parasite[2].

The role of *E. vermicularis* in relation to appendicitis is controversial and the aim of this study was to examine the incidence of *E. vermicularis* in appendices and to determine its possible role in the pathogenesis of appendicitis.

Patients and methods

This study included all appendices removed at Southmead Hospital, Bristol between 1980 and 1986. All the surgical specimens removed at operation from patients with clinical appendicitis, either as an emergency, or after an appendix mass had settled, were evaluated. Appendices removed *en passant* during the course of another intra-abdominal procedure were also studied. The gross specimens were preserved in formal-saline and three blocks were cut from each appendix—two transversely and one longitudinally. Each section, thus cut, was stained with haematoxylin and eosin and examined for inflammatory changes and the presence of *E. vermicularis* in the lumen. The inflammatory changes were divided, by the pathologist, into acute and chronic together with a group without any obvious abnormality.

Results

A total of 1529 appendices was examined, 1419 of which were obtained from patients with a clinical diagnosis of appendicitis (*Table 1*) and 110 obtained during the course of other surgical procedures. (*Table 2*). *E. vermicularis* was found in 38 appendices and these were all from patients with a clinical diagnosis of appendicitis. The incidence of *E. vermicularis* was 2·7 per cent in cases of clinical appendicitis and overall 2·5 per cent for all appendices removed during the 5-year period. There was no relationship between the presence of *E. vermicularis* and ethnic origin, age or sex of the patients.

In patients with clinical appendicitis (*Table 1*), *E. vermicularis* was most frequently identified in appendices with a chronic inflammation (14/169, 8·3 per cent) and in appendices without pathological changes (19/272, 7·0 per cent). In contrast, only 5 of the 978 cases of acute appendicitis (0·5 per cent) showed evidence of infestation. *E. vermicularis* was never seen in appendices removed during the course of another surgical procedure (*Table 2*).

Table 1 *Histological findings in appendices removed by surgery on the basis of a clinical diagnosis of appendicitis in the last 5 years at Southmead Hospital, Bristol*

	Acute inflammation		Chronic inflammation		Histologically normal	
Presence or absence of the pinworm in appendix	Present	Absent	Present	Absent	Present	Absent
Males	1	547	5	50	6	83
Females	4	426	9	105	13	170
Total	5	973	14	155	19	253

Table 2 *Histological findings in appendices removed in the course of another surgical procedure in the last 4 years at Southmead Hospital, Bristol*

	Acute inflammation		Chronic inflammation		Histologically normal	
Presence or absence of the pinworm	Present	Absent	Present	Absent	Present	Absent
Males	0	1	0	5	0	24
Females	0	1	0	24	0	55
Total	0	2	0	29	0	79

Discussion

Although the relationship of *E. vermicularis* to the pathogenesis of appendicitis has been investigated for many years, the influence of the parasite on the individual forms of inflammation is still unclear. Aschoff[3] found *E. vermicularis* in less than 1 per cent of examined appendices and suggested that they cause 'appendiceal colic' or symptoms resembling true appendicitis. His examination showed parasites only in the lumen of the appendix but no reactions in the tissue, except for slight mucosal bleeding, identical with that often seen after surgical trauma. More recent studies have maintained that the incidence of *E. vermicularis* is substantially higher in cases of chronic appendicitis than in acute inflammation[4,5] and this is confirmed in this present study. Other authors have also shown a high proportion of appendices with *E. vermicularis* in their lumina without pathological change[6], and this is also mirrored in our study.

Sterba and Vlcek[7] found that the number of granulomas in appendices infested with *E. vermicularis* far exceeded the number of granulomas in a control group of non-infested appendices. Indeed, Goldburt[8] noted that about 30 times more granulomas could be detected in appendices with a histotopographical examination of a complete series of sections as compared with the normal three sections. Thus many of the appendices with *E. vermicularis* in their lumina that appear histologically normal might, in fact, show evidence of granulomas if more sections were examined. Morgensen *et al.*[9] have shown that, apart from simply causing granuloma formation, *E. vermicularis* can also invade the wall of the appendix leading to inflammation.

The presence of *E. vermicularis* in the appendix may be related in the first instance to an 'appendiceal syndrome' with pain in the iliac fossa. Although an appendicectomy is clinically justified in these cases, the appendix appears histologically normal. In other cases, the parasite may bring about pathological changes in the appendix causing granuloma formation and eventually changes of chronic inflammation. Those appendices with only a few granulomas may be mistakenly grouped as histologically normal because only three routine sections have been examined. In some cases the parasite may actually penetrate the appendiceal wall before setting up an inflammatory reaction. All the above may cause symptoms leading to appendicectomy. The situation in acute appendicitis is less clear. In the few cases where *E. vermicularis* is found in association with acute inflammation it may be that the worm has been responsible for initiating the inflammatory reaction, although this study suggests that its presence may be coincidental.

In summary, *E. vermicularis* in the appendix is related to appendicular pain and chronic inflammation. In contrast there appears to be no relationship to acute appendicitis.

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Comparison of the local and systemic effects of sepsis in predicting survival

Progress in the study of sepsis has been hampered by the lack of a suitable system for grading its severity. Systems suggested for scoring sepsis have been based either on its systemic effects (APACHE II) or on a mixture of local and systemic variables (sepsis score). The APACHE II and sepsis scores were applied to patients with intra-abdominal sepsis of more than 3 days' duration, to determine if local or systemic factors were more important in predicting survival. Of 45 patients studied, 14 died. The sepsis score for non-survivors (median 21·5, range 11–32) was significantly higher than for survivors (median 14, range 10–26, $P<0{\cdot}05$*). There was overlap between the two groups, such that an individual score had no predictive value. The local component of the sepsis score was not significantly increased in non-survivors (*$P<0{\cdot}05$*), but the systemic component was (*$P<0{\cdot}05$*). The APACHE II score for non-survivors (median 24, range 15–38) was significantly higher than for survivors (median 12, range 3–21), and correctly identified 13 of the 14 fatalities. Both the systemic and non-systemic components (age and chronic disease) were significantly higher among the latter. The APACHE II was more effective than the sepsis score in predicting survival. We conclude that any system used for scoring sepsis should be based on systemic rather than local effects. At present the APACHE II score is preferred.*

Keywords: Sepsis, mortality, prediction, sepsis score, APACHE II

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Consistently predictive indicators of survival or death in severe sepsis would help to assess treatment regimens and would allow comparison between groups. Burns[1] and head injuries[2] are conditions in which the use of scoring systems has already led to a greater understanding of the disease process and its management.

The scoring of sepsis has been attempted using either complex haemodynamic variables[3], or simpler clinical and haematological data[4,5]. In 1983 Elebute and Stoner[4] reported preliminary results with a system which included the local and some systemic effects of sepsis. Of the 15 patients described, all those with a score above 20 died. Further validation by Dominioni *et al.*[6,7] in 135 patients, seemed to establish its utility, particularly when it was combined with changes in complement levels[8].

The APACHE (acute physiology and chronic health evaluation) score was first described in 1981 by Knaus *et al.*[9]). This system is based largely on physiological variables but includes a weighting for the patient's age and any pre-existing disease. Analysis of the results from initial studies led to the exclusion of variables with no independent influence on survival, and to the development of a modified form—APACHE II[10,11]. Although this was primarily for predicting survival among patients entering intensive care units, it appeared equally effective in sepsis[10]. Although APACHE I has been used in sepsis[12], no comparison has been made between the APACHE II (a system which is based on systemic variables) and the sepsis score (a system which is based on systemic and local factors).

The aim of this study was to use the APACHE II and sepsis score to determine whether local or systemic factors are more important in predicting survival.

Patients and methods

Patients with sepsis were entered into the study over a period of 3 years between 1983 and 1986. Sepsis was defined as the presence of pus in the chest or abdomen for more than 3 days. Scores were recorded daily and the highest obtained during the patient's illness was used for group comparison. The methods used were as those of the original authors[4,10], apart from modifications to the APACHE II as described by Bion[13]. This included the use of the haemoglobin rather than haematocrit, and the inspired oxygen concentration was incorporated when scoring the blood gases.

Results are given as median and range unless otherwise stated, with statistical analysis by the Mann–Whitney *U* test. For further analysis the sepsis score was divided into the local, and systemic effects of sepsis (temperature, secondary effects and laboratory data). Similarly the APACHE score was divided into systemic (clinical and haematological variables and the Glasgow coma scale) and non-systemic variables (age and chronic disease).

Results

Of the 53 patients studied, 8 had incomplete data available and were excluded. Two of these died. Of the remaining 45 patients 14 died during hospital admission. Although the median age for non-survivors (68 years) was higher than for survivors (57 years), the difference does not reach the conventional level of statistical significance ($P>0{\cdot}05$). All patients had sepsis present at the time of death, but one had a myocardial infarction and another an iatrogenic subclavian artery haemorrhage as contributing factors. The main associated diagnoses are listed in *Table 1*. Anastomotic failure and pancreatitis were the commonest causes of sepsis.

The sepsis score for those who died (median 21·5) was significantly higher than for those who lived (median 14, $P<0{\cdot}05$, *Table 2*). There was extensive overlap between the two groups (*Figure 1*), such that an individual score had no predictive value. Contrary to the findings of Elebute and Stoner,

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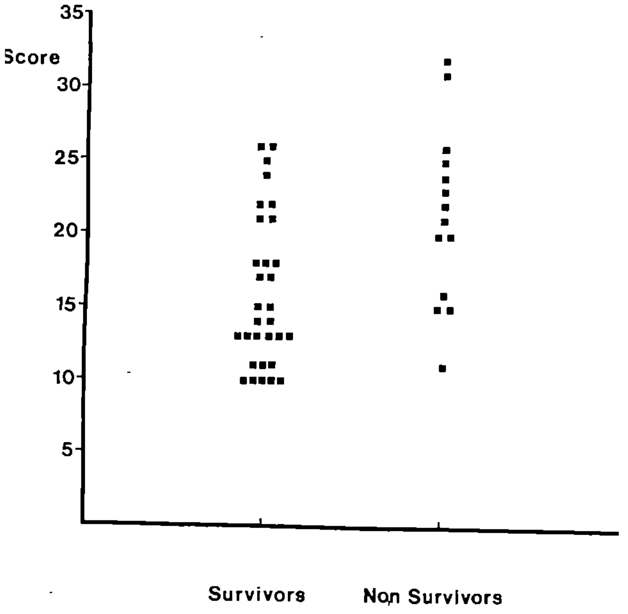
Table 1 *Diagnoses in the 45 patients studied*

Diagnosis	Number of patients
Anastomotic failure	13
Pancreatitis	12
Perforated viscus	9
Crohn's disease	2
Ulcerative colitis	3
Appendicitis	2
Trauma	1
Intrahepatic abscess	1
Miscellaneous	3

Table 2 *The local and systemic components of the sepsis score*

	Survivors ($n=31$)	Non-survivors ($n=14$)
Total sepsis score	14 (10–26)	21·5* (11–32)
Systemic	7 (2–15)	10·5* (1–19)
Local	8 (6–12)	10 (6–14)

Results are median and range. * $P<0·05$



igure 1 *The distribution of sepsis scores in survivors and non-survivors*

score of 20 was not a watershed of survival since 8 out of 15 uch patients survived. The systemic effects of sepsis were ignificantly increased in non-survivors ($P<0·05$), whereas local ffects were not ($P>0·05$) (*Table 2*).

The APACHE II score for non-survivors (median 24) was gnificantly higher than survivors (median 12) ($P<0·05$). The istribution of the APACHE II scores (*Figure 2*) for the two roups showed overlap in only one instance. Thus APACHE II redicted 13 out of the 14 non-survivors. Although the bulk of ie score was formed by the systemic variables which were gnificantly elevated in non-survivors (*Table 3*), the age and ironic disease weighting was also higher among nonirvivors.

iscussion

his study has demonstrated that the APACHE II score was ore effective than the sepsis score in predicting survival. If the two patients with other factors present at the time of death were excluded, the former was 100 per cent accurate in predicting survival. The superiority of the APACHE II may lie in its dependence on systemic variables. In addition, the APACHE II, unlike the sepsis score, has been developed and tested on more than 5000 patients.

Previous authors[7] have suggested that a rapidly increasing score is of more importance than the maximum score. This study has not considered this aspect because the intention was to determine whether groups of patients could be compared, and likely mortality rates predicted. The maximum score during the patient's illness should, if scoring is valid, represent the time of maximum threat to life, and consequently be a more powerful indicator of survival.

The sepsis score has been demonstrated to correlate with the metabolic effects of sepsis[14], and a score of greater than 10 is associated with the acute phase response[6]. In combination with our results, this may suggest that the sepsis score is more relevant to the grading of the metabolic effects of sepsis than to the prediction of survival.

Although in this study APACHE II accurately predicted 13 out of 14 fatalities, our series is too small to justify its use in individual patient management. Although a score may be used for following progress and possibly as an 'alerting' mechanism for the progress of sepsis, caution must still be urged in its application to decision making. In particular, and until we are satisfied that all appropriate attempts have been made to ensure that a patient lives, decisions to allocate specific treatments on

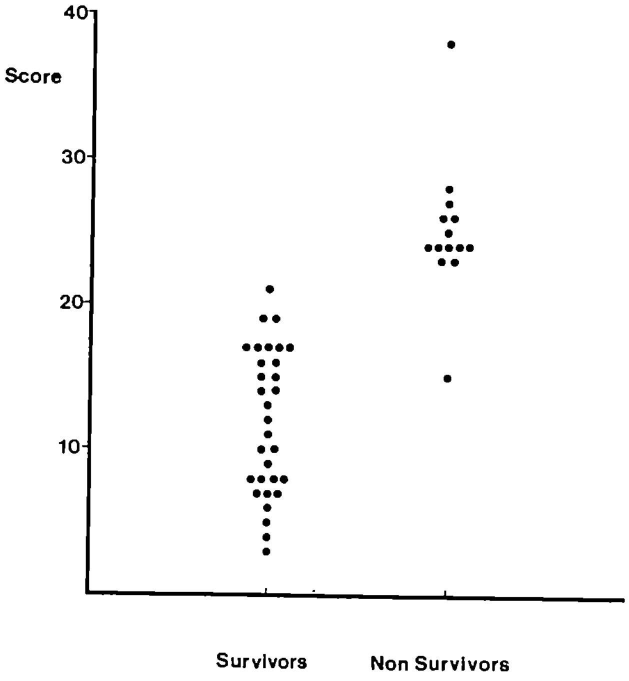


Figure 2 *The distribution of APACHE II scores in survivors and non-survivors*

Table 3 *The APACHE II score and its components*

	Survivors ($n=31$)	Non-survivors ($n=14$)
Total APACHE II	12 (3–21)	24·5* (15–38)
Systemic effects	8 (2–21)	21* (9–29)
Age+chronic disease	3 (0–6)	5* (0–11)

Results are median and range. * $P<0·05$

the basis of a patient's score[15] are inappropriate. We believe that our results in the management of severe surgical sepsis are improving and that cut-offs between survival and death will change. In the mean time, we have demonstrated that the APACHE II is a suitable scoring system for grading the severity of surgical sepsis. Its current value lies in group comparison within the structure of a controlled study and in investigating the physiological responses to varying degrees of sepsis.

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Fluoroscopic peroperative cholangiography: technique and associated radiation hazards

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The techniques specific to peroperative fluorocholangiography are discussed based on an experience of 632 cholangiograms and an estimation has been made of the associated radiation doses to staff and patients. Rapid and accurate information can be obtained during fluorocholangiography using appropriate techniques with acceptably low radiation hazards.

Keywords: Peroperative cholangiography, fluoroscopy, radiation hazards

The use of image intensification during peroperative cholangiography is now increasingly advocated and practised[1–3]. The techniques required differ from those proposed by Le Quesne[4] for three standard radiographs and these technical differences are discussed based on an experience of 632 fluorocholangiograms. In addition, an assessment is made of the associated radiation hazards to staff and patients.

Patients and methods

Seven hundred and seventy-two patients underwent cholecystectomy for gallstones in one surgical unit at Ashington Hospital, Northumberland, between February 1976 and January 1986. One hundred and forty of these patients either had cholangiograms performed using plain radiographs or, for a variety of reasons, no cholangiogram performed. The remaining 632 patients had fluorocholangiograms performed and the techniques discussed are based on the experience gained during these procedures.

Cholangiography was usually performed by securing a cholangiogram or ureteric catheter in the cystic duct with a haemostatic clip[5] and the image intensifier centred on the common bile duct after an infusion of 2–4 ml of contrast material (150 mg iodine/ml). In many patients this gave a satisfactory picture of the biliary tree but in others up to 20 ml of contrast was required. Failure to visualize the lower duct was often resolved after compression of the supraduodenal portion of the common bile duct or simply by waiting 10–30 s between short episodes of screening. The nature of uncertain filling defects could be clarified by varying the dilution of contrast material, by flushing the duct with normal saline or, most usefully, by compression of the duct with a long metal probe. It is helpful to observe the movements of filling defects as stones can be seen to collide and rebound, whereas air bubbles tend to distort, float and fractionate. A single plain radiograph was taken when screening was completed. In general, a decision whether or not to explore the common bile duct was based on the criteria recommended by Le Quesne[4], but the additional information obtained by screening of filling defects and poorly filled lower ducts made the significance of a dilated common bile duct less relevant.

A mobile fluoroscopy system (Philips BV22) was used with the image intensifier placed underneath the operating table and the X-ray tube above. An interchangeable radiotranslucent top was used, but a purpose-built operating table may be preferable. Typical technique factors were 80 kVp and 2–3 mA during fluoroscopy and 85 kVp, 20 mA, 0·4 s during radiography.

To assess the time involved in fluorocholangiography, 54 consecutive peroperative fluorocholangiograms were timed to determine both the screening time and the total time to perform the radiographic procedure.

A Perspex phantom (21 cm depth × 27 cm × 22 cm) was placed on an operating table to simulate a patient and the scattered radiation distribution adjacent to the table was measured during fluoroscopy and radiography. Measurements were made in a horizontal plane 45° to the midline of the phantom at eye and waist level, both external to and underneath a protective apron (equivalent to 0·125 mm lead). The calibration of the ionization chamber and the dosemeter used was traceable to the National Physical Laboratory.

The entrance dose to the Perspex phantom was measured for typical radiographic and fluoroscopic technique factors using an ionization chamber. These measurements were used to estimate patient skin entrance doses for each examination technique.

Results

The average overall time taken to screen each of the 54 patients and to take a single plain radiograph was 3 min but the average screening time was 70 s (range 10–120 s). This information, together with the data on scattered radiation dose rates was used to estimate the radiation dose equivalents to staff. *Table 1* is a summary of the estimated staff dose equivalents for an annual workload of 100 fluorocholangiograms. Doses have been estimated for a range of distances which are representative of the sites of different theatre personnel. The results presented in *Table 1* refer to technique factors specific to this particular hospital, although staff dose equivalents for an alternative set of technique factors and patient workload may be deduced from these data.

The accumulated readings recorded on a radiation badge worn by the operator (outside a lead apron) during the timed screening of 54 patients, was 2·71 mSv which approximates to 5·0 mSv for 100 procedures. Assuming the operator stood at a distance from the table which varied between 40 and 70 cm, the film badge reading correlates well with the dose equivalent of 5·6 mSv estimated for an operator standing at a distance of 50 cm (*Table 1*).

Estimated patient skin entrance doses for a single cholangiogram with different radiological techniques are given in *Table 2*†. The range of skin entrance doses for a single chest radiograph is shown for comparison[6].

Discussion

Fluoroscopy is becoming increasingly popular as a means of expeditious cholangiography. The required information can usually be obtained by screening for less than 2 min and the whole procedure completed in an average time of 3 min.

The recognition of stones is aided by a dynamic image and by

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† *The skin entrance doses to patients quoted in* Table 2 *are expressed as mGy as a measurement of the amount of energy released per unit mass of tissue; this unit is particularly useful in comparing different radiological techniques. The radiation hazards associated with occupational exposures are expressed as dose equivalent which takes into account other factors such as the type of radiation (although the correction or quality factor for X-rays is 1). The SI unit for dose equivalent is the Sievert (Sv) and the figures in* Table 1 *are therefore expressed as mSv.*

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Table 1 *Estimated annual staff dose equivalents for 100 examinations per year (mSv)*

Distance from centre of operating table (cm)	At eye level		At waist level (no lead protection)		At waist level (with 0·125 mm lead equivalent protection)	
	70 s screening +1 radiograph	70 s screening +3 radiographs	70 s screening +1 radiograph	70 s screening +3 radiographs	70 s screening +1 radiograph	70 s screening +3 radiographs
40	9·0	16	9·8	18	1·1	1·7
50	7·2	12	5·6	8·7	0·9	1·2
70	3·2*	4·8	2·4	4·0	0·32*	0·46
100	1·5	2·4	1·3	2·2	0·11	0·21
300	0·13	0·23	0·15	0·3	<0·05	<0·05

* Doses received per annum by a surgeon using recommended technique

Table 2 *Estimated patient skin entrance doses*

Examination technique	Dose (mGy)
3 radiographs	6·5
70 s fluoroscopy + 1 radiograph	18
70 s fluoroscopy + 3 radiographs	23
Chest radiograph	0·25–0·50

the facility to control the infusion rate and the dilution of contrast material. Probing of the duct by a long metal pointer during screening can be used to good effect to see if filling defects are compressible, to separate the terminal duct from a contrast-filled duodenum and to encourage the flow of the contrast into the terminal common bile duct. Some authors advocate the use of either amyl nitrite or glucagon with variable results[3,7,8], but we have no experience of this technique. The use of several radiographs in addition to screening[3] increases the radiation hazards to patients and staff and we advocate only one radiograph as a hospital record and rely surprisingly little on this for information.

Scattered radiation hazards adjacent to the operating table can be quite high. For instance, a surgeon who stands close to the operating table without protective clothing, whose technique involves 70 s screening and three radiographs could receive an annual waist level dose equivalent to 18 mSv. At this level, a surgeon would become a classified radiation worker[9]. Compliance with the Ionising Radiation Regulations[9] necessitates the wearing of suitable protective clothing against radiation by all theatre personnel. Wearing a protective apron (equivalent to 0·125 mm lead) may reduce the waist level radiation dose equivalent by a factor of approximately 8.

Theatre personnel should be aware that standing as far back as possible from the image intensifier produces a rapid fall off in radiation dose rates and most staff (using the technique and conditions described) should not receive an annual dose equivalent in excess of 0·25 mSv at waist level (*Table 1*). Although it is necessary for the surgeon to remain adjacent to the operating table to infuse contrast material during screening, it should be possible by the use of a 70 cm ureteric or cholangiogram catheter to stay at a distance of 60–100 cm from the image intensifier. This simple precaution could decrease the waist level dose equivalent to the surgeon to less than 0·4 mSv per annum (*Table 1*).

To place these figures in context, the whole body annual dose limit for a radiation worker is 50 mSv and for members of the public[9] it is 5 mSv. A typical figure for natural background radiation is 2 mSv per annum.

Usually the radiation eye dose equivalent received by a surgeon (*Table 1*) will be well below the limit of 150 mSv and the classified level of 45 mSv per annum[9]. Exceptionally, surgeons with a very high workload (250 cases per year or more), or who have additional radiation exposure, should consider wearing lead glasses or photochromic lenses and should make arrangements for monitoring of their eyes (in addition to wearing a dosemeter under the lead apron at waist level).

Depending on the technique used, estimated skin doses to patients were in the order of 18–23 mGy (*Table 2*). These doses are somewhat higher than for a simple postero-anterior chest radiograph[6]. While radiation hazards can be reduced by limiting the number of plain radiographs, 70 s fluoroscopy involves almost three times as much radiation to the patient as three radiographs (*Table 2*) and surgeons should therefore be aware of the necessity to reduce screening time to a minimum.

The use of short fluoroscopy periods, a minimum number of radiographs and a disciplined routine by theatre staff should ensure low radiation hazards to staff and patients. At the same time, rapid information can be obtained about choledochal filling defects and potential anatomical hazards.

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Salvage autotransfusion in aortic surgery: initial studies using a disposable reservoir

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Transmission of disease by allogeneic transfusion can be avoided using several techniques by which a patient receives his own blood. Sixty patients undergoing aortic surgery consented to salvage interoperative autotransfusion. A mean of 895 ml shed blood was reinfused under full heparinization, representing 12–74 per cent of total blood loss. Bank blood requirements fell from 4·9 units to 3·4. No important haematological or clinical complications were noted (including coagulation studies) but haemolysis was detected 4 h postoperatively by plasma haemoglobin levels of 0·05 ± 0·03 g/dl. This preliminary study confirms the applicability of salvage autotransfusion during elective vascular surgery by demonstrating an appreciable saving in bank blood transfusion (70 per cent).

Keywords: Autotransfusion, blood transfusion, aortic surgery

The potential adverse immunological and infectious consequences of homologous blood transfusion have been highlighted recently by increased tissue transplantation, transfusion-related hepatitis and acquired immune deficiency syndrome (AIDS)[1]. Concurrently a renewed interest in surgical salvage autotransfusion has occurred following the introduction of more efficient equipment[2–6].

Salvage autotransfusion, first performed in 1885, entails the collection of blood shed during surgery and its immediate intravenous reinfusion[7–11]. Advantages to the recipient are obvious: there is no risk of disease transmission or incompatibility. The blood is immediately available, normothermic and has a normal oxygen-carrying capability; but claims of improved coagulation properties over bank blood remain controversial. Reported complications include haemolysis and clotting factor activation[12–14]. Several centres have reported safe clinical use of salvage autotransfusion during various kinds of surgery but few have outlined the haematological consequences[15–18]. To date salvage should not be attempted if the operative field is contaminated by pus, urine, intestinal contents or tumour cells.

Changes in the administrative management of bank blood cross-match ordering and usage were summarized in a recent *British Medical Journal* editorial[19]. Further potential savings are evident if autotransfusion is safe especially during routine vascular surgery which is the largest single consumer for the transfusion services[20–24].

This report outlines our preliminary results of salvage autotransfusion during elective aortic surgery using a simple cheap, disposable plastic reservoir.

Patients and methods

Sixty consecutive patients (forty-six men, fourteen women aged 37–82) about to undergo elective aortic surgery consented to salvage autotransfusion. Thirteen of these in whom blood was electively not reinfused were used as controls. One patient underwent femoropopliteal grafting and his data were excluded leaving forty-six autotransfused aortic cases. Bank blood was available in the usual way but was normally not administered until autotransfusion had been completed. Salvage was only begun after systemic heparinization which was at an increased level (2 mg/kg body weight) to eliminate coagulation in the equipment and to prevent procoagulant activation[18,25]. After heparin reversal with the appropriate dose of protamine sulphate no further blood was salvaged or reinfused. This restriction (collection and reinfusion only under heparinization) of necessity reduced the potential amount of blood available to salvage. This was felt to be necessary in order to minimize the risk of initiating disseminated intravascular coagulopathy (DIC).

Blood collection was by a simple, plastic, disposable reservoir (Solcotrans, Cabot Ltd, High Wycombe, UK) using low suction pressure (75–100 mmHg) to minimize red cell trauma. At higher pressures increased cell destruction exposes more intracellular contents which may lead to activation of the coagulation cascade and may contribute to renal damage.

After the initial 15 cases a 50 mm extension tubing was placed between the sucker and reservoir for ease of use. An underwater seal (an adapted chest drain assembly) was included to act as a capacitance to reduce the effect of surges from the wall suction. Reinfusion using a 40 μm blood filter was commenced immediately and completed in all but two cases before starting bank blood transfusion. Maintenance of circulation with transfusion was by crystalloid and colloid fluids and did not differ appreciably from our normal practice.

Clinical outcome, total blood loss and transfusion requirements were recorded. Haematological estimations included haemoglobin, plasma free haemoglobin, white cell count and platelet levels. Plasma haemoglobin was measured using light absorption. Coagulation studies included a prothrombin index (expressed as a British corrected ratio (BCR) and International normalized ratio (INR)), activated partial thromboplastin time (APTT) and fibrin degradation products (FDP). FDP measurements were made using a semiquantitative method (Thrombo-Wellco test). Blood samples were taken pre-operatively, immediately after autotransfusion, and 4 and 24 h postoperatively. Sampling was also performed on blood shed into the wound prior to aspiration and from the reservoir before reinfusion. Renal and hepatic function was monitored using standard laboratory parameters. Results from 129 consecutive aortic replacements were also available as historical controls. Statistical analysis was by Student's *t* testing.

Results

Table 1 shows the demographic data.

Blood losses and salvage

Mean total losses were similar for autotransfusion patients (2620 ml) and contemporary or historical controls (2145 and 2260 ml) (P = n.s.). Salvaged blood volume (mean 895 ml) represented 36 per cent of the total loss (range 12–74 per cent). In the majority of cases maximum attainable salvage was not attempted in this initial study. The mean time for collection of salvaged blood was 35 min. Bank blood requirements were lower for the autotransfusion patients (3·4 units) when compared with both control groups (4·9 and 6·5 units) but statistical comparison was not attempted owing to the non-

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Table 1 *Demographic data of patients and controls in the study*

	Patients	Controls
	46	13
Age	65 (37–80)	68 (51–78)
Sex		
Male	37	8
Female	9	5
Aortic aneurysm	19	7
Aortic iliac occlusive disease	27	6

Table 2 *Blood losses and bank blood usage*

		Blood loss		Bank blood	
	No.	Mean loss (ml)	Range	Units	Range
Patients	46	2620	425–8500	3·4	0–12
Controls	13	2150	750–6000	4·9	0–10
Historical Controls	129	2260	—	6·5	—

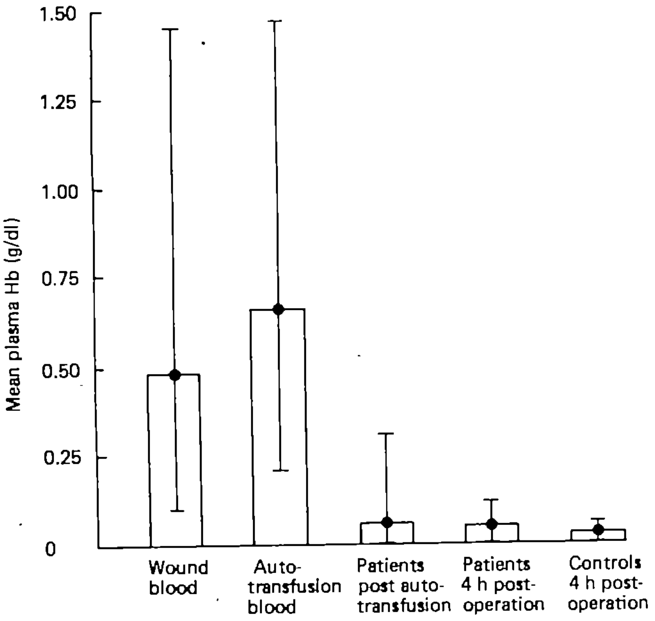

Figure 1 *Levels of haemolysis (plasma Hb) measured at various points during salvage autotransfusion (mean and ranges).* P=0·05

random nature of their selection (*Table 2*). Two patients (one aneurysm) received only autotransfused blood and all controls needed homologous transfusion.

Haemolysis

Appreciable levels of free plasma haemoglobin were noted in shed abdominal blood prior to aspiration (0·49 g/dl ± 0·4 s.d.) and this increased on salvage to 0·66 ± 0·39. The mean level immediately post-transfusion (0·06 ± 0·06) fell to only 0·05 ± 0·03 g/dl at 4 h (*Figure 1*). This appears consistent with some ongoing *in vivo* haemolysis. Plasma bilirubin levels 24 h postoperatively were similar in autotransfused patients and controls (22·3 ± 14·9 *versus* 21·8 ± 9·7) indicating other contributory sources of haemolysis such as at the graft surface and from shed abdominal blood. Visible haemoglobinuria was noted in five of the autotransfused group but none of the controls. Plasma haemoglobin levels at 4 h in the control group were 0·026 g/dl (*P* = n.s.). The effect of the addition of tubing to the system increased the amount of suction haemolysis significantly within the volumes autotransfused in this study (*Figure 2*). However, no difference in free plasma haemoglobin was detected in recipients immediately nor 4 h post-transfusion whether tubing had been used or not. Tubing should be kept to a minimum.

Changes in blood parameters were not unexpected (*Figure 3*). Platelet and leucocyte levels fell significantly on salvage aspiration and were associated with morphological cellular disruption and red cell crenation in the pretransfusion sample. These morphological changes were not noted in venous samples immediately post-transfusion and postoperative levels were similar for controls and autotransfused patients.

There were three deaths and no morbidity. One patient died from renal failure following massive intra-operative haemorrhage. It was not possible to judge whether autotransfusion played a part but platelet and FDP levels from

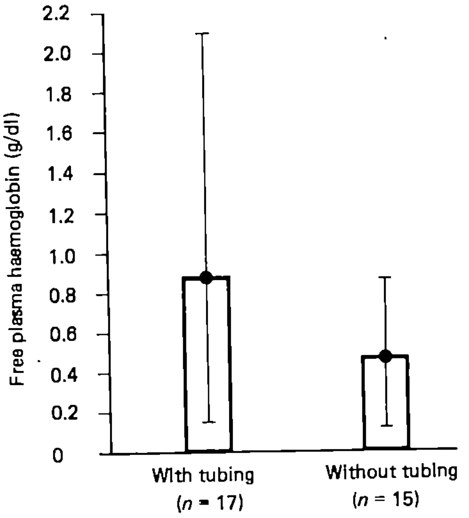

Figure 2 *Increased haemolysis using extension tubing* (P=*0·05*)

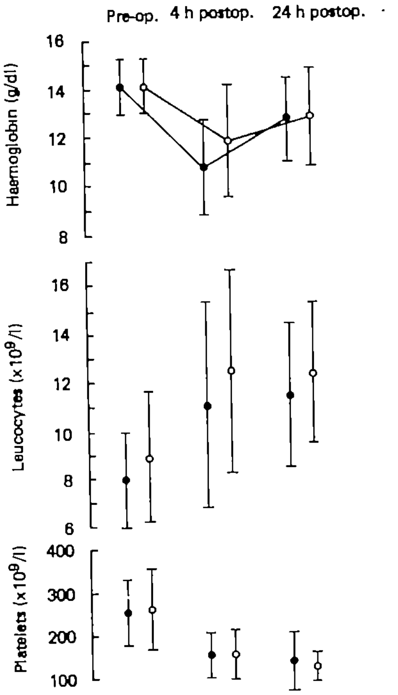

Figure 3 *Changes in blood parameters during surgery were not clinically important in either autotransfused patients* (●) *or controls* (○)

Table 3 *Changes in prothrombin time*

	Prothrombin index (INR)			
	Patients		Controls	
	No. tested	>1·3	No. tested	>1·3
Pre-op.	43	0	11	1
4 h postop.	32	10	7	6
24 h postop.	29	2	—	—

Table 4 *Results of coagulation studies: fibrin degradation products*

Range (μg/ml)	Patients	Controls
<10	5	2
10–20	5	2
20–40	5	2
40–80	5	1
80–160	1	0

this patient were reported as within normal limits. Of the other two, one suffered a fatal postoperative myocardial infarction and the other developed trunk and buttock gangrene with no internal iliac blood flow.

Coagulation studies

No untoward changes in the basic coagulation parameters were noted although a higher proportion of patients in the control group had abnormal prothrombin times (INR>1·3) 4 h postoperatively (*Table 3*). FDP levels were measured in 21 cases (*Table 4*) and were raised in 16. However only six reached levels normally regarded as clinically significant in this unit and were not associated with a clinical coagulopathy. In the control group FDP levels were measured in seven cases and were elevated in five. No clinical coagulopathy was noted.

Renal function

Only one case of renal failure was noted in the patient mentioned above. Urea and creatinine levels were otherwise similar for the autotransfused patients and controls.

Discussion

Elective aortic surgery, particularly aneurysm repair, produces the highest routine cross-matching load after cardiac surgery for the blood transfusion service[21]. Defensive over-ordering may occur and result in unnecessary cross-matching of large volumes of bank blood. Thus elective peripheral vascular operations are an ideal vehicle for evaluating autotransfusion techniques since there may be significant and rapid operative blood loss to salvage. Here the potential savings in bank blood usage are the greatest.

To date there is insufficient data in the literature to define the causes of DIC during vascular surgery with or without autotransfusion. Salvage autotransfusion appears safe under heparin 'cover' which should be maintained until infusion is complete.

This preliminary study has confirmed the clinical and haematological safety and applicability of salvage autotransfusion for elective aortic surgery. Despite the voluntary restriction initially to 1000 ml and then up to a maximum of 1500 ml autotransfusion there has been an appreciable reduction in the use of allogeneic blood (70 per cent). Further randomized studies are required to define its possible wider peroperative role as an adjunct to bank blood usage.

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Twenty-four-hour ambulatory oesophageal pH monitoring

Sir

The recent article by Dr D. F. Evans (*Br J Surg* 1987; **74**: 157–61) is an interesting exposition of the uses and potential pitfalls of this technique. However, as this review article could influence readers' choice of pH monitoring equipment, it is essential that the following points are clarified.

When describing the characteristics of the miniature glass electrode M1506 (Microelectrodes Inc.) the author states that it is 'particularly useful for paediatric measurements although its response time is slow and its cost relatively high'. We have recently completed a study comparing the electrode operating characteristics of the M1506 with those of the GK2801C combined glass electrode (Radiometer, Denmark) and the antimony electrode 0011 (Synectics, Sweden) under different conditions[1]. As can be seen in *Table 1*, the response of the M1506 is extremely fast. If, when measuring response time, both sensing and reference electrodes are transferred between solutions, their combined response will be obtained. Studies conducted in this way with a slow reference electrode could account for the slow response time quoted by Dr Evans.

Two points arise from the 98 per cent response time values shown in *Table 1* of Dr Evans' review. Firstly, in our experience the selection of a 98 per cent level to establish response time is too high to be useful. In this region of the voltage/time graph, very small voltage changes are taking place over a relatively long time span and the choice of a 98 per cent response time is therefore highly susceptible to error. Secondly, Dr Evans mentions neither the pH range nor the direction over which response was measured and both can markedly affect the result. While we realize that this Table is only intended as a guide, the information provided could be misleading. In our own study using a 10–90 per cent response time[1], a clear difference emerged between the two glass electrodes, with antimony being slower than either (*Table 1*). As with glass, plastic electrodes show response time variation dependent on electrode geometry (J. M. Rawlings and M. L. Lucas, unpublished observations). It must be emphasized that when comparing response times of different electrodes they must be tested under identical conditions which should be clearly stated. If these criteria are observed, it would be seen that the response time of plastic electrodes is similar and not superior to that of glass[2], in contradiction to the information given in Dr Evans' table.

Referring again to *Table 1* in Dr Evans' paper, it is difficult to understand what the author means by 'Sensitivity (mV)'. Sensitivity is defined as the change in potential difference which occurs over a decade change in hydrogen ion activity and is expressed as mV/pH unit. We can only assume that Dr Evans is referring to 'range' and not 'sensitivity' here, that the '0–30' value for glass should read '0–300' and that the '0–500' value for antimony should read '−500–0'. If so, it should be pointed out that this gives no indication of sensitivity and simply indicates the operating range of a particular electrode, which is dependent on internal factors and can be compensated for if required, using measuring devices which have offset facilities.

The author makes a valid point that not all electrodes are compatible with data loggers. While this is true, it cannot be due to a 'tenfold difference in voltage output' since typical values for antimony are: 100 mV at pH 1 and −400 mV at pH 7, and for glass +350 mV at pH 1 and 0 mV for pH 7. The voltage span over this pH range is therefore very similar for glass and antimony. The choice of equipment should be determined by the input impedance of either the voltmeter or data logger input amplifier. An insufficiently high impedance (cf. Dr Evans' recommendation) here will lead to collapse of the electrode voltage.

Table 1 *Response times of the three types of electrodes under different conditions*

From	To	10–90% Response time (s)		
		Glass (Micro-electrodes Inc.)	Glass (Radiometer)	Antimony (Synectics)
Buffer pH 7	Buffer pH 1	<0·5	<0·5	<0·5
Buffer pH 1	Buffer pH 7	0·5 ±0·1	0·8±0·1	3·4 ±0·8
Buffer pH 1 (unstirred 22°C)	Buffer pH 7 (unstirred 22°C)	3·25±1	20·8±8	160±24
Duodenal juice pH 6·5	Buffer pH 1	<0·5	<0·5	<0·5
Gastric juice pH 1·5	Buffer pH 7	1·0 ±0·2	0·8±0·1	4·5 ±0·7

Values are mean ±s.e.m. Six electrodes of each type were studied. All experiments were performed in stirred solutions at 37°C except where indicated to contrary in parenthesis

This paper usefully reviews the operating characteristics of the Radiopill. The reader, however, can only make an informed choice of the most suitable electrode and system for his needs if the operating characteristics of the alternatives are accurately presented. Dr Evans' sources of information in this area seem to have let him down.

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M. L. Lucas
K. E. L. McColl

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UK

1. McLauchlan G, Rawlings JM, Lucas ML, McCloy RF, Crean GP, McColl KEL. Electrodes for 24-hour pH monitoring—a comparative study. *Gut* 1987 (In press).
2. Rawlings JM, Lucas ML. Plastic pH electrodes for the measurement of gastrointestinal pH. *Gut* 1985; **26**: 203–7.

Inguinal hernia

Sir

We read the case report presented by Levy and Ebbs (*Br J Surg* 1987; **74**: 363). We wish to point out that giant hernias are not infrequently seen in many parts of Africa. The diagnosis of gastric scrotal hernia can readily be made pre-operatively without recourse to X-ray by auscultation of a scrotal splash after swallowing fluid[1].

It is recommended that for huge hernias the abdominal cavity is expanded over 2–3 weeks by induction of a pneumoperitoneum before reduction and repair of the hernia is carried out.

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C. T. Faranisi

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1. Davey WW, Strange SL. The stomach as a content of inguinal and femoral herniae. *Br J Surg* 1954; **41**: 651–8.

Removal of a retained Foley catheter

Sir

Mr MacDermott has mentioned yet another way of deflating recalcitrant balloons (*Br J Surg* 1987; **74**: 25). In this context, I would like to stress one point which is not universally known. Foley balloons should be filled with sterile distilled water and never filled with saline. When filled with saline, the fluid has a tendency to egress out of the fine channel which leads to the balloon. Crystals of sodium chloride deposit in this channel and make subsequent deflation of the balloon difficult. Changing over to distilled water will reduce the number of times that the balloon does not deflate.

J. Talati

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Non-specific acute abdominal pain

Sir

I would like to comment on two points made by Gray and Collin (*Br J Surg* 1987; 74: 239–42) in their useful summary of the information currently available on the syndrome of non-specific acute abdominal pain (NSAP).

It is difficult to agree with their statement that 'no prospective study has been reported of the detailed symptomatology and physical findings displayed by patients' with NSAP. During 1965 we studied the clinical features of all children referred to this hospital with acute abdominal pain. We recorded prospectively the symptoms, signs and subsequent progress of all the 315 patients so referred, most of whom came in with a provisional diagnosis of acute appendicitis[1]. At the end of that year, when the completed pro formas were analysed, we were surprised to find that as many as 119 children had settled without treatment and had gone home in 24–48 h. These we compared with the 114 children who had suffered proven acute appendicitis. This study was continued and 2 years later we were able to compare 398 children with acute appendicitis and 323 children who had recovered from what we called non-specific abdominal pain[2]. Principal symptoms and signs in the two groups were set out in a table, and some marked differences were demonstrated. Another year of prospective recording, 1973–1974, produced very similar results[3].

These clinical features of NSAP (and especially the early disappearance of localized tenderness in about one-third of the patients) may allow some to be safely sent home after a period of observation in the accident and emergency department. However, some discretion must be exercised in pursuing Gray and Collins' suggestion that, by making an early diagnosis of NSAP it is possible to 'forestall admission to hospital and minimize the waste of resources'. It can be difficult, initially, to decide whether some children have early acute appendicitis (especially when the appendix lies behind ileum or just over the brim of the pelvis) or whether they will prove to have NSAP. They require a period of active observation extending over some hours, and this often entails admission, especially when they have travelled some distance. Several re-examinations can be required before surgical disease can be excluded[3].

Recognition of the syndrome of NSAP has already led to a reduction in the number of emergency appendicectomies and hospital admissions, but it is still a diagnosis which should only be made at the time when observation has shown that it is safe to send the patient home.

P. F. Jones

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1. Winsey HS, Jones PF. Acute abdominal pain in childhood: analysis of a year's admissions. *Br Med J* 1967; **1**: 653–5.
2. Jones PF. Acute abdominal pain in childhood, with special reference to cases not due to acute appendicitis. *Br Med J* 1969; **1**: 284–6.
3. Jones PF. Active observation in management of acute abdominal pain in childhood. *Br Med J* 1976; **2**: 551–3.

Authors' reply

Sir

We are grateful to Mr P. F. Jones for drawing attention to the omission of his paper from our review. His study[1] does indeed report the clinical features in children with abdominal pain not due to appendicitis. The bulk of patients with NSAP are adults, however, the peak incidence being in young women[2,3]. It would be incautious to assume that the symptoms and signs, aetiology and natural history of NSAP in adults are the same as in children.

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J. Collin

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1. Jones PF. Acute abdominal pain in childhood, with special reference to cases not due to cute appendicitis. *Br Med J* 1969; **1**: 284–6.
2. Rang EH, Fairburn AS, Acheson ED. An enquiry into the incidence and prognosis of undiagnosed abdominal pain treated in hospital. *J Prev Soc Med* 1970; **24**: 47–51.
3. Jess P, Bjerregaard B, Brynitz S *et al*. Prognosis of acute non-specific abdominal pain. *Am J Surg* 1982; **144**: 338–40.

Perforated duodenal ulcers

Sir

The recent leading article by Raines and Devlin (*Br J Surg* 1987; 74: 81–2) makes clear recommendations on the management of perforated duodenal ulcers. We believe however that a 'new breed' of perforated duodenal ulcers is occurring as a result of non-steroidal anti-inflammatory drug (NSAID) ingestion. These require a different therapeutic approach to 'classical' duodenal ulcer perforation. In a recently completed 3-year prospective study in South Cheshire[1] we have identified 110 perforated duodenal ulcers. Sixty-three (57 per cent) of these were using a NSAID at the time of their perforation. Only 48 per cent of the 63 had a past history of dyspepsia compared to 70 per cent of the 47 not using a NSAID ($\chi^2 = 7{\cdot}14$, $P < 0{\cdot}001$). Despite the lack of dyspepsia many patients had ulcers that, at operation, appeared to be chronic. It is not appropriate to treat all of the patients in the NSAID group by simple oversew and H_2 antagonists.

When faced with a patient using NSAIDs it is necessary to question why the drug is being used. Clearly, if the NSAID is being used as an analgesic and future long-term therapy can be avoided, the patient should undergo simple closure and treatment with H_2 antagonists until the ulcer is healed. A different problem is posed by patients with a severe arthritic condition in whom long-term NSAID therapy will be required to enable the patient to have a reasonable quality of life. This group should be considered for an emergency definitive ulcer operation even in the absence of a previous dyspeptic history. It should be remembered that long-term concurrent administration of H_2 antagonists has not been shown to prevent NSAID induced ulcer complications.

The problem is certainly an interesting one, particularly as a definitive ulcer operation does not prevent NSAID induced ulcer complications, although it is likely that they are reduced. When treating a patient with a perforated duodenal ulcer it should be remembered that there are three types: the acute, the chronic and the drug induced.

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1. Armstrong CP, Blower AL. Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulceration. *Gut* 1987 (in press).

Colon 'cast' in a patient with ischaemic colitis

Sir

We read with interest the case described by Gregory and Barrett of spontaneous passage of a full thickness colon 'cast' in a patient with ischaemic colitis and an abdominal aortic aneurysm (*Br J Surg* 1987; 74: 436). They remark that the remaining cavity served as a conduit for flatus for 15 h.

We are currently managing a similar patient but whose granulation tissue-lined track acted as a conduit for flatus and 12 stools daily for 8 weeks before transfer to this hospital! Ten weeks earlier this 55-year-old physician with diabetes mellitus had severe lower abdominal pain and passed blood rectally. Radiological features were similar to the described case. The patient was treated as for ulcerative colitis and after episodes of septicaemia and pulmonary embolism passed a 68 cm full-thickness colon cast 2 weeks later. After 2 months he was transferred to this country. He had tenesmus and diarrhoea. Sigmoidoscopy showed mucosal ulceration to 2 cm from the dentate line. At operation a 4 cm infrarenal abdominal aortic aneurysm was found. Division of the inferior mesenteric artery showed organized thrombus within. The descending colon and sigmoid colon were represented by a granulation lined tube. The muscle coats of the rectum were present while the mucosa had been shed. It is interesting to note that the muscle of the rectum is supplied by the middle rectal artery (internal iliac artery) while the mucosa is supplied from the superior rectal (inferior mesenteric artery)[1]. In addition, there is a critical point in the marginal artery at the splenic flexure between the left and right branches of the left colic artery[2]. The rectum and track in the left paracolic gutter were excised.

After division of the middle colic and right colic arteries (in order to gain length) the ascending colon supplied by a marginal vessel from the ileocolic artery was anastomosed to the anus using the stapler and a loop ileostomy constructed. He remains an in-patient.

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1. Williams PS, Warwick R, eds. *Gray's Anatomy*, 36th edn. London: Churchill Livingstone, 1980: 717–20.
2. Griffiths JD. Surgical anatomy of the blood supply of the distal colon. *Ann R Coll Surg Engl* 1956; **19**: 241–56.

Peripheral gangrene associated with β-blockade

Sir

We read with interest the case report by Stringer *et al.* of peripheral gangrene associated with β-blockade (*Br J Surg* 1986; **73**: 1008) and wish to make the following comments.

This case is similar to that reported by Vale *et al.*[1] in that the patient developed symmetrical gangrene of the feet 4 days following metoprolol therapy for tachydysrrhythmia and heart failure. The main lesson that these cases demonstrate, we feel, is that β-blockers may exacerbate limb ischaemia in patients where limb perfusion pressure is already impaired acutely (in this case due to left ventricular failure, with compensatory elevated peripheral vascular resistance maintaining blood pressure). Whether the reduction in limb blood flow is related to further fall in cardiac output consequent upon β-blockade (associated with α-mediated increase in peripheral vascular resistance) or to a direct blockade of β_2 receptors (with unopposed α-constriction) or perhaps both, remains uncertain[2,3].

The reason that this is not seen more frequently with β-blockers is that they are not usually given to patients with heart failure, especially in the acute situation. These two cases outline a further hazard of β-blockers in patients with impaired left ventricular function. The problem may become more frequent if β-blockers are given early in suspected myocardial infarction to limit infarct size (ISIS[4]).

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1. Vale JA, Van de Pette SJ, Price TML. Peripheral gangrene complicating beta-blockade. *Lancet* 1977; **ii**: 412.
2. White CdeB, Udwadia BP. Beta adrenoreceptors in the human dorsum and hand and the effects of Propranolol and Practolol on venous sensitivity to noradrenaline. *Br J Clin Pharmacol* 1975; **2**: 99.
3. Breckenridge A. Which beta-blocker? *Br Med J* 1983; **286**: 1085–8.
4. First international study of infarct survival—collaborative group. Randomised trial of intravenous atenolol among 16027 cases of suspected acute myocardial infarction. ISIS—1. *Lancet* 1986; **ii**: 57–65.

Overwhelming postsplenectomy sepsis

Sir

Your recent journals reflect the still uncertain importance of overwhelming postsplenectomy sepsis (OPSI) in adults, following splenectomy for trauma (*Br J Surg* 1987; **74**: 310–13 and 343–5). Unfortunately, little attention has been directed towards quantifying the serious and potentially fatal complication of secondary splenic rupture.

The alleged incidence of OPSI following splenectomy for trauma in adults is 0·2–0·3 per cent, thus the loss of even a single life from secondary splenic rupture would counter any theoretical protective advantages conservation may offer against OPSI. Splenic conservation is successful in less than one-quarter of patients in whom it is attempted and all surgeons who have attempted conservation will be familiar with delayed rupture that may occur in up to one-third of cases.

It may be that the risk of death from OPSI in adults is little different from that consequent to secondary splenic rupture.

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Secondary aorto-enteric fistulae

Sir

Two recent papers (*Br J Surg* 1986; **73**: 875–8 and *Br J Surg* 1987; **74**: 256–9) have highlighted the problem of secondary aorto-enteric fistulae involving prosthetic grafts.

Umpleby, Britton and Turnbull (1987) favoured the North American approach of graft excision and extra-anatomic reconstruction, while Thomas and Baird suggested that in the absence of gross graft infection simple closure of the fistula may be all that is needed. The latter authors emphasized that even when the graft is removed the aortic stump can go on to rupture or fistulate.

I have recently performed simple closure of a fistula on two occasions on the same patient. A 78-year-old Ukranian man had an inflammatory aortic aneurysm replaced by a Dacron® bifurcation graft in April 1985. He presented in June 1986 with a massive haematemesis due to an aortojejunal fistula at the left side of the upper anastomosis. The fistula was taken down and the vascular defect closed with Prolene®. He made a good recovery but, despite the graft being covered with omentum, he re-presented in February 1987 with a further life threatening haematemesis. This time he had an aortoduodenal fistula at the right side of the upper anastomosis. The vascular defect was again simply closed and covered with omentum and so far he remains well. On both occasions proximal vascular control was obtained by using an intraluminal Foley catheter, the gut was closed with two layers of continuous catgut and antibiotics were given peri- and postoperatively. Due to the inflammatory nature of the original aneurysm excision of the graft would have been hazardous and time consuming with a long period of ischaemia to his legs. Direct suture, on the other hand, proved to be relatively quick and easy.

Clearly the type of procedure chosen should be tailored to the operative findings. This case, along with the four similarly treated by Thomas and Baird, emphasizes that simple closure of the vascular defect in secondary aorto-enteric fistulae may be all that is required.

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Orthopaedic staples to control aortic bleeding

Sir

We read with interest J. G. Mosley's article (*Br J Surg* 1987; **74**: 319). We agree that an infected aortic graft causing massive aortic bleeding is a difficult problem which necessitates excision of the prosthesis. However, we are unable to envisage any situation where control of an aortic stump need be achieved by 'hammering an orthopaedic staple into the vertebral bodies'.

This solution involves the risk of introducing infection into the vertebral bodies. Our orthopaedic colleagues can attest to the risks of implanting metal in infective situations. Not only is sepsis promulgated, but the metal works loose. It would not be unreasonable to expect an incidence of recurrence of aortic bleeding.

Furthermore, J. G. Mosley advocates the use of metal staples since 'dense adhesions may prevent a clamp being applied to the aortic stump'. One can only suppose that the technique advocated is 'blind' and, therefore, entails risks of damage to nearby structures, e.g. inferior vena cava, renal arteries.

We would suggest that the approach to the problem entails preliminary control of the proximal aorta prior to dissecting the anastomotic area. If there is a stump of aorta available below the renal arteries suture closure is always possible. If there is not then stapling must endanger the renal arteries and is in our view contra-indicated and accurate suturing under vision is even more important. The surgeon must be prepared under those rare circumstances to revascularize one or both kidneys.

Mosley relates an anecdotal experience involving removal of an end to side aortic graft and stapling proximal and distal ends. Again we would suggest that the appropriate management involved sutured closure of the aortic arteriotomy, retaining the possibility of autogenous reconstruction or endarterectomy if needed.

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Book reviews

Urologic Complications

F. F. Marshall. 260 × 180 mm. Pp. 451 + xiv. Illustrated. 1986. London: Wolfe Publications Limited. £62.00.

This book is a handsomely produced, well illustrated, 451 page compendium of current American urological practice. The first 101 pages deal with non-surgical topics which I imagine would be of greater interest to very junior surgical staff. The remainder of the book deals with urological surgical aspects. I was surprised to see a large amount of space given over to detailed surgical techniques pertaining to standard urological operations. Indeed, only a fraction of the book describes complications and their management, in some cases rather superficially. In defence of this editorial policy it must be said that prevention is better than cure. The real question is: who is this book written for? I think it will be good reading for urological fellowship and state boards examinations. It is less useful for a consultant faced with a serious complication, who seeks a detailed course of action or description of a surgical technique, which is rather a pity. The book does however have a splendid reference section at the end of each chapter and unlike many American books contains references to international and not only American papers.

Anyone reading this book will certainly broaden his urological horizons, but it is probably best suited to an institutional library rather than a personal copy, bearing in mind the vast choice of reference books now available to the urologist and their not inconsiderable cost.

R. A. Miller

A Colour Atlas of Reducting Operations for Lymphoedema of Lower Limb

N. L. Browse. 265 × 195 mm. Pp. 79. Illustrated. 1986. London: Wolfe Medical Publications Limited. £17.00.

This series of colour atlases has become renowned and Norman Browse's addition is of the highest standard. There are few surgeons who could produce such a wide range of illustrations and these act as the backbone for a very practical atlas. The nuances of technique are well explained and each step is clearly defined—too many operative textbooks seem to leap across the problems without admitting their presence. The surgery is also put into perspective by the reminder, both at the outset and towards the end, that most patients can be treated conservatively and that good palliation is the aim. Since lymphoedema is a relatively rare disease there are few surgeons who require the excellent advice in this well presented book but hospital libraries should have it available for those that do.

J. N. Wolfe

Advances in Surgery. Volume 20

J. A. Mannick. 235 × 155 mm. Pp. 352 + xiv. Illustrated. 1987. London: Wolfe Medical Publications Limited. £46.00.

This book is Volume 20 in a series which reviews, in depth, 11 topics of general surgical interest. Each review is extensive, comprehensive and well referenced. Most general surgeons will find at least one article of specific interest to their own practice although controversy and disagreements are inevitable.

I found the reviews on the management of penetrating abdominal trauma, small bowel Crohn's disease, and acute pancreatitis to be particularly valuable; each providing useful and practical tips for conditions in which correct surgical decision making is of vital importance.

I. Taylor

Lecture Notes on Fluid and Electrolyte Balance. Second Edition

S. M. Willatts. 215 × 130 mm. Pp. 370 + xiii. Illustrated. 1986. Oxford: Blackwell Scientific Publications. £9.80.

Dr Sheila Willatts admits that few wax lyrical about fluid and electrolyte balance. Her book, however, provides up-to-date practical information about normal and abnormal fluid and electrolyte balance in a concise and very readable style. In addition, there are chapters on fluid balance in the surgical patient, nutrition and renal disease. Special circumstances that are considered include diabetes mellitus and burns. The final chapter has useful notes on peripheral and central intravenous infusion.

I thoroughly recommend this book to all students and hospital doctors, especially those who will admit that they do not know the difference between hyponatraemia and pseudohyponatraemia.

G. T. Royle

1986 Year Book of Cancer

R. C. Hickey, G. F. Saunders and R. L. Clark, eds. 235 × 155 mm. Pp. 494. Illustrated. 1986. London: Wolfe Medical Publications Limited. £43.00.

I cannot envisage anyone buying this book. Any clinical oncologist of any worth will have already read and probably taken reprints of the papers, included in this book, which are relevant to his/her practice.

The editor states in his introduction that the book carries forward the publication's initial mission; to improve the scientific understanding of cancer and, thereby, to improve therapy, lessen suffering, and decrease disability. Certainly these are great ideals but I do not believe that this book will do much to bring the information from the bench to the bedside.

No one can fault the selections in the various systems that have been culled from the world medical literature. What one has to ask is the use of putting all these abstracts of all these different papers in one book. It is also difficult to find one's way round the book if looking for a specific subject. For instance, if one was interested in reading about malignant melanoma, papers appear in four different sections.

Probably the one very useful feature of the book is the list of additional reading at the end of each chapter. The references as well as a short synopsis are very useful. The short summaries at the end of each of the papers is, in the main, unhelpful.

I suppose departments will buy this book for reference but I cannot see it having a place on any individual's shelf. It seems to me to fall between two stools—it is neither text book nor reference book.

D. Rosin

Handbook of the Spinal Cord. Volumes 4 and 5: Congenital Disorders and Trauma, Infections and Cancer

R. A. Davidoff. 157 × 235 mm. Pp. 823. 1987. New York: Marcel Dekker, Incorporated.

This publication is made up of the latest two volumes in a series devoted to the spinal cord. The volumes under review deal with congenital disorders, trauma, infection and cancer, while the previous three volumes dealt with the pharmacology, anatomy and physiology. This book reminds one of the curate's egg. While some of the individual contributions are excellent, the Editors must take at least some, if not all, of the blame for the fluctuation in quality. The first impression was that this 'broad and comprehensive survey' was less than complete. Such comments as 'I will not deal with the local histopathology of traumatic cord lesions as this subject has been dealt with thoroughly in several recent reviews', helped to reinforce this impression. The contents of the Volume were puzzling and it was difficult to reconcile a chapter on cervical spondylosis, a chronic degenerative condition, included in the section on congenital disorders and trauma; while I am not sure of the relevance of toxic, metabolic and deficiency diseases affecting the spinal cord to infections and cancer.

The chapters on spinal cord syndromes and spinal cord trauma were, at best, complementary and, at worst, repetitious. While the former provided a less than adequate description of the various clinical syndromes affecting the spine following injury, the latter chapter was more an appreciation of a particular type of spinal injuries bed. In pleasant contrast, the chapter on infections of the spine was well presented and an excellent review of the subject. It clearly outlined the reasons for surgical management and quite rightly condemned laminectomy in the treatment of vertebral osteomyelitis, complicated by spinal cord compression. The chapter on systemic cancer involving the spinal cord was less clear; this reflects the current muddled thinking on the surgical management of this condition. The first half of this chapter was an excellent description of the clinical entity and rightly emphasized the origin of the spinal problem as being in the anterior vertebral elements in the majority of cases. Despite this, the authors then went on to describe surgical decompression by a posterior approach often involving a wide laminectomy; they even go on to remark, later in the chapter, that a laminectomy often gives disappointing results. This is the old chestnut—where there is anterior spinal disease, particularly with vertebral destruction, any surgical approach involving destruction of the posterior elements will compromise further the stability of the spine and may even render it totally unstable.

From the surgical point of view these volumes were rather disappointing; they were more a clincal appreciation of the various conditions rather than a description of their surgical management.

M. Smith

Notices and announcements

Meetings

16–21 August 1987
17th World Congress of the Society of Orthopaedic and Traumatological Surgery
Munich, FRG
Information: Dr W. Baur, Orthopädische Klinik, D-8501 Schwarzenbruck/Nuremberg, FRG

24–28 August 1987
The Prevention and Management of Organ Failure
London, UK
Information: The Conference Organizer, Critical Care '87, BJHM, Battersea Business Centre, 103–109 Lavender Hill, London SW11 5QL, UK

31 August–4 September 1987
Surgical Efficiency and Economy
Lund, Sweden
Information: Professor S. Bengmark–SEE, Box 5121, S-220 05 Lund 5, Sweden

4–6 September 1987
IMLS. Quality Assurance Symposium
Liverpool, UK
Information: Mr D. Kilshaw, Department of Pathology, Arrowe Park Hospital, Arrowe Park Road, Upton, Wirral, Merseyside L49 5LN, UK

6–8 September 1987
An Introduction to Laser Surgery
Sheffield, UK
Information: Mrs V. M. Coomer, Regional Conference Centre, Lodge Moor Hospital, Sheffield S10 4LH, UK

9–11 September 1987
Clinical Controversies in Inflammatory Bowel Diseases
Bologna, Italy
Information: Organizing Secretariat, SO.GE.PA.CO. Spa. piazza Constituzione, 5/c, 40128, Bologna, Italy

14–18 September 1987
International Meeting on Tumour Necrosis Factor and Related Cytokinins
Heidelberg, FRG
Information: Professor H. Kirchner, Cancer Research Centre, Institute of Virus Research, Im Neuenheimer Feld, 6900 Heidelberg, FRG

15–18 September 1987
The British Society of Gastroenterology Jubilee Meeting
London, UK
Information: The Administrative Secretary, The British Society of Gastroenterology, 3 St Andrew's Place, Regent's Park, London NW1 4LB, UK

20–25 September 1987
32nd World Congress of Surgery
Sydney, Australia
Information: Secretariat, GPO Box 2609, Sydney, NSW Australia 2001

21–25 September 1987
Fourth ELMS Course in Biomedical Research Technique for Surgeons in Training
Southampton University Department of Surgery, UK
Information: ELMS, University Surgical Unit, General Hospital, Southampton SO1 6HU, UK

5th October 1987
An International Symposium of Second Generation Lithotripsy for Urologists and Hospital Administrators
London, UK
Information: Ms Pauline Sleight, BDI Conferences Ltd, Kensington Business Centre, 9–11 Kensington High Street, London W8 5NP, UK

11–16 October 1987
Annual Clinical Congress of the American College of Surgeons
San Francisco, California, USA
Information: American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-2797, USA

15–17 October 1987
Fourth Meeting of the European Chapter of the International Union of Angiology
Brussels, Belgium
Information: Madame D. Shanni, Administrative Secretariat, ECCO, Rue Vilain XIIII, 17a, B-1050 Brussels, Belgium

18–24 October 1987
Recent Advances in Pancreaticobiliary Surgery
Glasgow, UK
Information: Professor D. C. Carter, University Department of Surgery, Queen Elizabeth Building, Royal Infirmary, Glasgow G31 2ER, UK

22–23 October 1987
First British Symposium on Surgical Stapling
Manchester, UK
Information: Conference Coordinates, Confer House, 69 Kingston Road, New Malden, Surrey KT3 3PB

24–25 October 1987
Autumn '87 Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, c/o Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

1–6 November 1987
Progress in Cancer Management: Radiotherapy and Chemotherapy
London, UK
Information: Courses Department, The British Council, 65 Davies Street, London, W1Y 2AA, UK

5–6 November 1987
Annual Joint Scientific Meeting of the American Pancreatic Association and the Pancreas Cancer Section of the NCI Organ Systems Program
Chicago, Illinois, USA
Information: Midge Kellerhaus, American Pancreatic Association, Department of Surgery, M580, University of Missouri Medical Center, Columbia, MO 65212, USA

11–13 November 1987
First International Congress in Oral Cancer
Singapore
Information: Dr N. Ravindranathan, The Secretariat Department of Oral Surgery, Faculty of Dentistry, National University of Singapore, Kent Ridge, Singapore

15–18 November 1987
All Americas Health '87
Tampa, Florida, USA
Information: Denis Beckett, Fairs and Exhibition Ltd, 51 Doughty Street, Gray's Inn, London WC1N 2LB, UK

16–20 November 1987
Fourth International Symposium on Cardiorespiratory Emergencies
Rotterdam, The Netherlands
Information: Dr Omar Prakash, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands

1–2 December 1987
First International Symposium on Aids and the Surgeon
London, UK
Information: Ms Pauline Sleight, BDI Conferences Ltd, Kensington Business Centre, 9–11 Kensington High Street, London, W8 5NP, UK

Notices

Volunteers needed for 3–6 weeks surgical appointments in overseas Mission Hospitals. Please contact: Mr M. W. Flowers, Accident and Emergency, General Infirmary, Great George Street, Leeds LS1 3EX.

Leading article

Br. J. Surg. 1987, Vol. 74, September, 763–764

Surgical technique

Surgery is a technical subject, and consequently the details of technique are of note. *The British Journal of Surgery* has traditionally published articles outlining the steps of an operation, exemplified by the classic operative descriptions of Goligher[1]. Such articles now occupy a lesser role in the Journal because rarely are new operations described, although technical modifications continue to be published and appreciated by surgical readers. Despite the undoubted importance of surgical technique, possible variations in the excellence of that technique have rarely been taken into consideration in the analysis of risk factors in surgery, although variations in outcome of the same surgical procedure has been commented upon in the context of a clinical trial[2]. The paper by Pettigrew and colleagues (pages 791–794) highlights the importance of surgeon related variables in the assessment of risk factors, and concludes that operative performance is the main factor in the development of postoperative complications. Surgeons recognize that many of the complications after surgery are operator dependent; they are probably more important than prognostic formulae, and the use of perioperative nutritional support. Pettigrew's study confirms that after operation the surgeon can identify significantly more high risk patients because technical events were the most important identifiable cause of postoperative morbidity and mortality, and therefore should be assessed in future studies of the outcome of surgical procedures. The innate assumption of the experienced surgeon is that the way forward to improving perioperative outcome is not only an improvement in the pre-operative fitness of the patient but also an improvement in operative skills. The term operative skill is not limited to manual dexterity, for this quality can be taught and acquired, but also to the application of technical surgical research to the operating room, such that techniques which have been shown by audit and clinical trial to be less good can be discarded, and replaced by methods of proven value.

In no area of surgical expertise has this been better shown than in the making and repair of the abdominal incision. Since the seminal paper by Jenkins[3] the repair of the abdominal wound has been a major cause of concern to the surgeon. This issue highlights some of the problems still associated with the abdominal wound. Paes and colleagues (pages 822–824) suggest that the traditional curve around the umbilicus is unnecessary while Brennan *et al.*[4] point out that the time saving of the medial paramedian incision is rewarded by a higher incidence of incisional herniae. Illustrations like *Figure 1*, page 824 are all too common reminders of patients seen in surgical outpatients, yet the cause varies for, if the hypothesis presented by Krukowski and Matheson is to be accepted, this particular hernia was not due to defective technique or suture material, but to the presence of a non-absorbable suture correctly chosen and correctly placed creating over a period of months a 'button-hole' in the abdominal wall. Thus, the way to avoid this late problem is to use a delayed absorbable suture material as suggested by the same authors and their colleagues (pages 828–830) in their trial comparing polydioxanone and polypropylene. Similar conclusions are reached by Wissing *et al.*[5] who showed that, although continuous nylon has the lowest incidence of incisional hernia, its use is associated with more wound pain and suture sinuses which more than offset the slightly higher incidence of incisional herniae in the polydioxanone group (13·2 *versus* 10·3 per cent). My own preference is for interrupted polydioxanone using a standard mattress suture to ensure apposition of the sheath. The characteristics of such a mattress suture may well be improved by the loop mattress technique described on pages 820–821 by Gault and colleagues. Their technique can be tested in clinical practice to determine whether the technique is an advance which prevents the 'cheese wire' effect of the tense wound with possible reduction of the 'button-hole' effect and hence incisional herniae. By acquiring knowledge, through the clinical studies outlined above, surgical technique and skill can be improved.

Surgical technique not only includes the way surgeons accomplish a task, but also the materials they use and the instruments designed as surgical aids. Materials used in surgery are changing, yet despite the advance in suture material, for instance, and the ability to test these materials in the laboratory[6], the older materials

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such as linen with their many disadvantages remain popular sutures in clinical practice. Perhaps this inability to change our technical aids masks the low importance given to this branch of surgery in recent years, and the discouragement of the younger innovative surgeon to develop new surgical aids. This Journal has tried to encourage technical development by the publication of these contributions under the Surgical Workshop series. The technical aids described in this issue may well be known to some, disliked by others and even ridiculed by a few, but hopefully these ideas may help one or two to change their technique, if only to relieve the assistant of the unnecessary task of holding the liver retractor during cholecystectomy less well than a mechanical aid (page 826). The time has come when surgeons must re-examine their surgical technique, and devise new methods, preferably taking advantage of new technology. Is it still necessary to tie knots in difficult corners when heat sensitive absorbable synthetic materials are available for some types of bonding?

Technique is important, understanding of audit and data analysis is essential, and the ability of the surgeon to keep abreast of developing technology is necessary. Correctly, many bemoan that these attributes are not tested in our asessment of surgical trainees. However, a start has been made by our surgical colleagues in Holland who are grappling with this problem (M.H. Gough, personal communication) by aptitude testing and seconding a part of the selection process of surgical trainees to Personnel Consultants who are seeking to assess the suitability of the surgical trainee to the changing demands of surgery. Perhaps in the current debate on surgical examinations, more consideration should be given to selection and subsequent training with greater emphasis on technical excellence, such that technical factors and surgeon-related variables are less significant as perioperative risk factors.

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Review

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Heller's myotomy for achalasia: is an added anti-reflux procedure necessary?

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Literature review (1970–85) indicates excellent or good results following Heller's operation in 89 per cent of 5002 patients. The overall mortality was 2·8 per cent with a reoperation rate of 2·8 per cent. When the operation was done through an abdominal incision, gastro-oesophageal reflux was almost twice as common as when it was done through a thoracic incision, regardless of whether an anti-reflux procedure was performed.

Keywords: Achalasia, Heller's myotomy

Achalasia is due to decreased numbers or absence of ganglion cells in Auerbach's plexus between the inner circular and outer longitudinal muscle layers. In the normal oesophagus there are almost no nerve cells in the submucous Meissner's plexus so that a mucosal biopsy is useless for diagnosis. The physiological abnormalities are: absent peristalsis in the body of the oesophagus and abnormal relaxation in the gastro-oesophageal sphincter, which never amounts to a total absence of relaxation—achalasia—but only to incomplete relaxation and not always in response to every swallow. The oesophagus fills up with food and fluid leaving the contents to trickle into the stomach under the influence of simultaneous contraction waves and gravity. The air that accompanies a normal bolus does not enter the stomach and an absent gastric air bubble is diagnostic. The resting pressure in the smooth muscle sphincter is either normal, as measured by non-perfused open tip manometry, or above normal if perfused. This perfused pressure is the preferred methodology now and represents a squeeze response to pressure increments caused by the perfused fluid in the sphincter. It is the manometric equivalent to cardiospasm which is often used as a synonym for achalasia—the Greek word for failure to relax[1].

The treatment for achalasia is based on the principle that there is an abnormal sphincter which causes obstruction, and that weakening, but not destroying it completely, improves oesphageal emptying even though the underlying pathology itself cannot be changed. Dilatation of the lower oesophagus and its treatment by a whalebone probang were described by Willis in 1672[2,3]. The first successful surgical procedure was performed by a German surgeon, Ernest Heller, on 14 April 1913 through a laparotomy and consisted of a double myotomy[4]. Zaaijer, a Dutch surgeon, modified this by using a single myotomy incision in 1923[5]. The weakening of the gastro-oesophageal sphincter by a single incision approach through the abdomen or chest is the present surgical procedure of choice. There are two main complications: recurrent dysphagia due to an incomplete myotomy and gastro-oesophageal reflux. In the last 15 years there has been an increased number of reports of reflux after a Heller's myotomy and many authors have advocated the routine addition of an anti-reflux procedure. In spite of this, the majority still do a simple myotomy and obtain good results. The purpose of this article is to review the recent literature to see whether there was any reason to add the anti-reflux procedure, whether its necessity was due to a different technique of making the cut in the muscle which destroyed rather than weakened the sphincter, and why some surgeons have good results with a simple myotomy and very little subsequent gastro-oesophageal reflux.

Review of the literature

A review in 1980 reported 4500 patients[6], whereas previously the situation was summed up by Ellis and Olsen in their classic 1969 monograph based on 1906 patients[2]. The present paper is based on 5002 patients reported in 75 papers[7–81] (*Table 1*). Some papers with incomplete data have been excluded but the number cited represents some 90 per cent of all the cited literature from 1970 to 1985.

Diagnosis

The diagnosis of achalasia may be made by analysing clinical symptoms, radiology, cineradiography and oesophageal manometry[82]. Although manometry and oesophageal pressure studies are important and essential according to some[22,26,28,56], they have been employed in only 5 per cent of the series reported[13,23,26,28,30,33,45,55,56,58,60,62,76]. Oesophagoscopy was used in 12 per cent[10,13,14,17,18,21,28,33,46,51,60,71,75,81]. Other tests such as acid perfusion and pH measurements[13,15,19,30,62], cineradiography[51] and pharmacological tests (mecholyl)[34] were rarely used. Of specific relevance to the present study, the associated abnormalities of hiatus hernia (0·5 per cent)[14,57] and peptic ulcer (< 0·3 per cent) were rarely found pre-operatively. Approximately 43 per cent of the patients reported had been dilated before being submitted to definitive surgery[10,13,27,28,34,51,58].

Surgery

Since the first Heller's myotomy in 1913 and Zaaijer's modification in 1923, both by the abdominal approach, numerous different procedures have been introduced. In this review 56 per cent of the patients had the myotomy done through a thoracotomy. Some authors employed both the thoracic and abdominal approach[37,73]. The different anti-reflux procedures with reference to the authors using either a thoracic or abdominal approach are listed in *Table 2*.

Associated procedures such as proximal gastric vagotomy[30], truncal vagotomy[63] and pyloroplasty[17,31,37,54,63] have also been used. Other authors have proposed a complete incision through the oesophageal wall and reconstitution of the oesophagogastric junction with the gastric fundus[37,63,70,83] or Y–V cardioplasty[37]. Approximately 50 per cent of the patients had an added anti-reflux operation. The mark IV Belsey repair was the most widely used anti-reflux procedure by thoracic surgeons (21 per cent) and the anterior fundoplication was mostly employed by abdominal surgeons (36 per cent).

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Table 1 *Collected data from 75 papers (1970–85)*

First author	Year	Country	Patients				Approach*	Anti-reflux procedure	Deaths (%)	Results (%) (excellent and good)	Reflux (%)	Reoperations
				Sex		Mean age (years)						
			n	Male	Female							
Adebo[7]	1980	Nigeria	36	25	11	34·5	T	—	2·8	94	6	2
Akuamoa[8]	1971	Denmark	101	61	40	40	A	—	—	91·5	8·5	
Anyanwu[9]	1982	Nigeria	30	21	9	36·6	T	—	—	96·3	0	
Arvanitakis[10]	1975	USA	23	14	9	54·4	T	—	—	91	0	
Barker[11]	1971	England	30	15	15	41	T	—	—	90	16·6	3
Belsey[12]	1972	England	149				T	+	1·3	90		16
Bjorck[13]	1982	Sweden	63	29	34	43	T	—	—	88	12·6	
Black[14]	1976	England	108	56	52	47·5	A	+	—	65·5	18·5	4
Borgeskov[15]	1970	Denmark	52	24	28	42	T	—	—	75	15	3
Boulez[16]	1981	France	103				A	—		95	17·5	
Cabrero-Gomez[17]	1982	Spain	50	19	31	40	A	+	—	86·4	6	5
Caminiti[18]	1975	Italy	27			58	T	—		88	7·4	
Castrini[19]	1982	Italy	40	27	13	44	T	—	—	95	2·7	2
Coan[20]	1971	Italy	21	10	11	35	T	+	—	90		
Coloni[21]	1975	Italy	124				T	—	—	87·6	6·4	
Csendes[22]	1975	Chile	20	11	9	45·2	A	+	—	95	0	
De La F. Perucho[23]	1977	Spain	45	20	25	32·8	A	+	—	78·5		
Dotsenko[24]	1973	Ethiopia	17			30	T	+	—	90		
Dotsenko[25]	1984	Russia	52	18	34		T	+	—	95	5	
Duranceau[26]	1982	Canada	12	6	6	44	T	+	—	95	0	
Effler[27]	1971	USA	100	35	65	12–74	T	+	—	87	3	4
Ellis[28]	1984	USA	113	49	64	45	T	—	—	94	3·5	
Fekete[29]	1977	France	370				A	+	—	85		55
Gallone[30]	1982	Italy	14	8	6	45	A	+	—	95	0	
Gavriliu[31]	1975	Romania	256				A	+	—	84·1		
Giovinetto[32]	1978	Italy	24				A	+	—	87·5	12·5	
Goulbourne[33]	1985	Scotland	65	33	32	40	T	—	—	80	4·6	
Grimes[34]	1970	USA	50			47	T	—	—	78	6	
Harley[35]	1976	Wales	65				T	—		96·5	35·2	
Heil[36]	1980	Germany	13				A	+	—	100		
Hirashima[37]	1978	Japan	21				A	—	—	80		
Hollender[38]	1977	France	22				A	+	—	90	10	
Jamieson[39]	1984	Canada	36	18	18		T	+	—	95	2·7	4
Jara[40]	1979	USA	145	57	88	40–60	T	—	—	89	24	9
Jezioro[41]	1977	Poland	21				A	+		90	9·5	
Kessler[42]	1980	Germany	49				A	+	2	90	0	
Kinoshita[43]	1981	Japan	19				A	+	—	73		
Lagache[44]	1970	France	53					—	—	90	5·6	
Lens[45]	1980	Holland	12	8	4		T	+	—	100	0	
Mabogunje[46]	1983	Nigeria	20	11	9	20–40	A	—	—	80	5	
Maillet[47]	1973	France	72				A	+	—	96		
Mansour[48]	1976	USA	38				T	—	—	80	23·6	
Mehta[49]	1974	India	75	42	33		T	—	1·3	86·7	8	
Menguy[50]	1971	USA	6				A	+	—	100		
Menzies-Gow[51]	1978	England	102	51	51	45	T	—	—	80	13·7	5
Moreno G-Bueno[52]	1981	Spain	64	30	34		A	+	—	94·2	5·8	
Mullard[53]	1972	England	100				T	—	—	96	7	
Muralidharam[54]	1978	India	90	60	30		T	—	1·1	92·3	3·1	
Murray[55]	1984	USA	21	12	9	8–74	T	+	—	95	0	
Nelems[56]	1980	Canada	32			46	T	+	—	90	12·5	14
Nemir[57]	1971	USA	74				T	—	1·35	75	17·5	11
Okike[58]	1979	USA	468	220	248	51	T	—	—	94	3	3
Orringer[59]	1976	USA	3				T	+	—	100		
Pai[60]	1984	USA	36	18	18	43	T	+	2·8	94	11·1	4
Petrovsky[61]	1972	Russia	113				T	+		79·7	7·1	
Peyton[62]	1974	USA	14	8	6		T	+	—	80	29	
Rees[63]	1971	USA	84	50	34	48·4	T	+	—	90	8·3	6
Ribet[64]	1975	France	75				A	+	—	79	14	
Rossetti[65]	1978	Switzerland	63				A	+		95		
Ruland[66]	1981	Germany	57							90	9·8	
Sariyannis[67]	1975	England	48	17	31	50·7	T	—	—	95·8	8·3	3
Schomacher[68]	1978	Germany	25	12	13	42	A	+	—	95		
Sery[69]	1982	Poland	204				A	+	—	85		
Shevchuk[70]	1983	Russia	31				A	+	—	95	6·4	
Stein[71]	1985	Zimbabwe	25						—	90		
Stipa[72]	1976	Italy	162				A	—	—	85	22	
Tomlinson[73]	1981	Australia	74	29	45	48	T	+	1·4	91·4	8·5	
Uchida[74]	1981	Japan	20				T	+		95		
Veiga-Fernandes[75]	1981	Portugal	15				A	+	—	100	0	
Viard[76]	1983	France	90	40	50		A	+	—	87·6	11	4
Vossschulte[77]	1972	France	19				A	—	—	100		
Yon[78]	1975	USA	24			40–50	T	—		85	20·8	

Table 1 *Collected data from 75 papers (1970–85) (continued)*

First author	Year	Country	Patients n	Sex Male	Sex Female	Mean age (years)	Approach*	Anti-reflux procedure	Deaths (%)	Results (%) (excellent and good)	Reflux (%)	Reoperations
Yu Yong-Xian[79]	1983	China	44	18	26		T	+	—	90		
Wenzel[80]	1972	Germany	36				A	—	2·8	90		
Wingfield[81]	1972	England	27	11	16	37	T	—	—	80	11·1	5

* T, thoracic; A, abdominal

Table 2 *Anti-reflux procedures with reference to authors using either a thoracic or abdominal approach*

Mark IV Belsey repair[13,39,45,48,55,56,60,62,72,74,75,76]
Nissen fundoplication[26,42,60,65,68,75]
Lateral fundoplication[17,32,52,76]
Anterior fundoplication[22,25,30,31,37]
Diaphragmatic pedicled graft—Petrovsky[24–26,61,79]
Hiatal diaphragmatic reconstitution[14,27,54,81]
Collis repair[14,20,38,56,59]
Allison repair[60]
Hill repair[75]
Others[17,20,31,36,41,43,59,69,70]

Table 3 *Incidence of postoperative reflux*

	Heller's myotomy alone	Heller's myotomy and anti-reflux procedure
Thoracotomy	7·7%	7·3%
Laparotomy	13·2%	7·4%

Results

Relief of dysphagia is the aim of a Heller's myotomy and this was achieved with 'excellent' or 'good' results in 89 per cent ± 7·2 (mean ± s.d.) (range 65·5–100 per cent) (*Table 1*). The terms 'excellent' or 'good' were taken from the published data and should mean that the patients could swallow solid food without difficulty. It was a totally subjective assessment in the majority and there was no practical and agreed difference between the words excellent and good. These represented early results but late review in 65 per cent of these patients gave a range of between 60 and 94 per cent excellent and good results. The term 'late' meant review at between 1 and 36 years. The overall mortality rate, calculated from the papers in *Table 1*, was 0·2 per cent. Higher mortality rates occurred in small series of patients[7,42,60,80]. Other reported rates from large series in the literature were 1·4 per cent from 1906 cases collected before 1969[2], 0·7 per cent from 1669 cases collected from 1968 to 1975[84] and 1·1 per cent from 611 cases collected between 1967 and 1975[38]. The most important early complication was perforation of the mucosa during myotomy, usually closed immediately with careful suture of the mucosa. This complication was found in 1·1 per cent of the patients in this review. Perforation of the mucosa led to an oesophageal fistula and pleural empyema in 0·4 per cent. Other postoperative problems occurred such as pneumonia and atelectasis (1·8 per cent), wound infection (0·8 per cent) and phlebitis (0·5 per cent).

Gastro-oesophageal reflux was the most frequent late complication. The true incidence is difficult to establish because it depends on surgical approach, length of myotomy, associated pathologies, length of follow-up and methods of assessing postoperative reflux[1,28,82,85]. A range of between 0 per cent and 29 per cent was discovered in this review during the early postoperative period with an average of 8·6 per cent ± 7·0 (mean ± s.d.). *Table 3* shows the incidence of reflux after thoracotomy and laparotomy with and without an additional anti-reflux procedure, calculated from those papers with complete data (65 per cent). All four groups had the same percentage of patients (about 90 per cent) with excellent or good results. The terms 'excellent' and 'good' were used in most papers even though reflux occurred, so obviously all reflux was not considered equal. Diagnosis of reflux was not equally accurate either, with the method being variously symptom analysis, radiology and pH measurement. Oesophagitis was not a term used accurately and was taken to mean oesophagitis diagnosed by visual appearance or that seen by microscopy. There were not sufficient data to calculate whether any specific anti-reflux procedure prevented reflux more than another, although the single commonest procedure was fundoplication followed by the mark IV Belsey procedure. Nor was it possible to state that a specific procedure would be more likely to be followed by dysphagia. About twice the number (13·2 per cent) had reflux with a Heller's myotomy done through a laparotomy than through a thoracotomy (7·7 per cent) and this percentage became lower (7·4 per cent) when an anti-reflux procedure was added to the abdominal approach. Statistical analysis showed that the difference between the laparotomy group without an anti-reflux procedure and the others was significant ($\chi^2 = 26{\cdot}573$, $P < 0{\cdot}05$).

Reoperations were performed in 146 out of the 5002 patients (2·9 per cent), but this figure must be an underestimate because most series did not include this information in their follow-up data. Eight reoperations were done for an incomplete myotomy, five for relief of dysphagia due to the anti-reflux procedure, three for leakage and the remainder, the majority, for reflux or peptic stricture. There was not enough information to assess the incidence of postoperative dilatation necessary either for an incomplete myotomy or a peptic stricture. Simple dilatation to FG 50 with a bougie relieved dysphagia due to an incomplete myotomy on the gastric side[2] so that most reoperations were done for uncontrollable reflux[86].

Peptic stricture, a late complication of oesophagitis due to gastro-oesophageal reflux, was found in about 3 per cent of the patients with complete data. Re-operations to treat peptic stricture were performed with various techniques: oesophagogastrostomy[17,57,60], oesophagogastrectomy[29,40,51,76], cardioplasty[14,27,29,40,57,63,81], jejunal or colon interposition[17,57,60,67] and subtotal gastrectomy[57].

Discussion

It was not the purpose of this review to discover whether a Heller's myotomy is better than various methods of oesophageal dilatation. This has been discussed in other papers[6,11,58,66,85,87], although the matter is still controversial. The main purpose was to discover why some surgeons add an anti-reflux procedure to their routine myotomy. Many authorities perform a Heller's myotomy through the thoracic approach with one myotomy cut, and no added procedure and produce good results[2]. It would appear that those who advocate additional anti-reflux procedures obtain too much reflux following a routine myotomy and seek to reduce it to acceptable levels. But is their myotomy performed properly, is the approach correct, is the phreno-oesophageal ligament preserved, and would they be better advised to do the myotomy correctly in the first instance?

In the abdominal approach the phreno-oesophageal ligament has to be divided to expose enough of the lower oesophagus to do an adequate myotomy proximally. The incision through a laparotomy is usually anterior whereas it is more lateral through the thoracic approach. Some authors, believing in the gastric sling fibres which run obliquely round the lower oesophagus, state that their preservation is important and that their destruction is the cause of reflux. The experimental evidence refuting this theory is discussed in Ellis and Olsen's monograph[2]. With an abdominal incision the distal cut usually extends further onto the stomach than with a thoracic approach whereas Ellis[2,28,86] recommends only cutting 0·5 cm distal to the mucosal gastro-oesophageal junction. This can be done in the thoracic approach with minimal disruption of the phreno-oesophageal ligament through a longitudinal incision. In the chest there is no need for full mobilization of the oesophagus by cutting the ligament circumferentially. The authors are fully aware of the controversy about this phreno-oesophageal ligament and whether it exists or not. Its destruction probably leads to reflux; respecting and preserving it is more likely to leave the normal anti-reflux mechanism intact while at the same time achieving the weakening, not the total destruction, of the zone of elevated pressure. This weakened sphincter in its correct position can prevent reflux, without an added anti-reflux procedure. Do those who use these additional procedures believe that the flap valve effect produced is more important than the low pressure sphincter?

It is appreciated that the poor secondary clearing of the lower oesophagus after a myotomy occurs because lack of peristalsis is a feature of the disease and is not altered by surgery. This reflex emptying after gastro-oesophageal reflux is slow, weak and inefficient; it results in pooling of acid in the lower oesophagus and that is why procedures such as fundoplication can cause dysphagia when done at the same time as a myotomy. It seems odd to do a Heller's myotomy which weakens the sphincter and then add a procedure that is said to increase sphincteric pressure.

In summary, the abdominal approach for a Heller's myotomy results in more reflux than a thoracic approach. There is abundant experimental evidence to show that extending the incision onto the stomach increases reflux[2,28,40,84,86]. This is discussed in great detail by Ellis and Olsen[2] and no recent research has challenged the experimental results. The sphincter is only 4 cm long physiologically and it would seem logical to weaken it by a limited incision both proximally and distally; extending the cut 7–8 cm proximally is unnecessary and may weaken lower oesophageal clearing. Incomplete distal myotomy or a myotomy that had reunited were rare. The technique of burrowing laterally between the muscle and mucosa for 180° to allow mucosa to pout through and prevent the muscle joining up is well accepted. Extension of the muscle cut to only 0·5 cm distal to the gastro-oesophageal mucosal junction is sufficient to perform an adequate myotomy yet prevent reflux. This epithelial junction can be seen when the mucosa has been mobilized and is the only accurate way of limiting the distal incision. Since good results can be obtained by a correctly done Heller's myotomy through the left chest, the conclusion to be drawn from this review is that additional anti-reflux procedures are only needed to compensate for an incorrectly done myotomy or are unnecessary.

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Node dissection in gastric cancer

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Three hundred patients who underwent absolute and relative curative gastrectomy and lymph node dissection for gastric cancer were reviewed with respect to postoperative mortality; proportion of patients with node involvement according to the extent of dissection; number of metastatic nodes dissected according to the extent of dissection; accuracy of macroscopic evaluation of node involvement and microscopic node involvement according to tumour location. If more nodes were dissected the proportion of patients with node involvement and the total number of metastatic nodes increased; conversely within R_0 and R_3 the extent of dissection did not affect postoperative survival. Finally when the presence and extent of node involvement was only macroscopically evaluated, the patients were classified incorrectly in 9·5 per cent of the N_0 group and 20·2 per cent of the N_1 group. The data suggest that lymph node dissection may be useful in the treatment of gastric cancer, and within the extent studied the employment of this procedure does not affect the postoperative mortality.

Keywords: Gastric cancer, lymph node dissection, lymph node metastasis

Although the incidence of gastric cancer is reported to have decreased in recent decades, the disease still represents the major cause of death by cancer in Japan, and in some countries in Latin America and northern Europe[1]. Recently in Japan there has been an improvement in the life expectancy of patients undergoing curative gastrectomy[2–4]. This improvement has probably been due in part to the active employment of diagnostic methods and a mass survey system to detect patients with early gastric cancer[3–6].

The importance of the lymphatic system in the spread of gastric cancer has been acknowledged for many years[7,8], and extensive regional lymph node dissection is also believed to have contributed to the improved survival of patients with advanced gastric cancer[2–4,9–12]. However, the results obtained in the treatment of gastric cancer in countries other than Japan have been disappointing, and there is no agreement about the usefulness of lymph node dissection[13–17].

With regard to the efficacy of extended lymph node dissection, it is difficult to demonstrate any benefit on survival rate without a randomized controlled study. For this reason, the aim of the present report was only to study the relationship between the extent of lymph node dissection and the number of metastatic nodes found, the proportion of patients with node involvement, and the postoperative mortality. Furthermore, we have studied the accuracy of intra-operative assessment, and the percentage of nodes involved relative to their location.

Patients and methods

Three hundred patients who underwent 'absolute' and 'relative' curative resection according to the 'Japanese Rules for the Gastric Cancer Study' were studied[18]. All the patients were operated on between 1973 and 1983 in the Department of Surgery II of Kanazawa University. Among the patients studied, 121 patients had lesions characterized as 'early' and 179 patients had advanced gastric cancer. When the tumour involved the proximal stomach, total gastrectomy with splenectomy and pancreatic tail resection was the operation more commonly performed, while when the tumour involved the middle or distal stomach subtotal gastrectomy was the standard operation. In eight patients with pancreatic involvement but without distant spread, pancreaticoduodenectomy was performed (*Table 1*).

In relation to lymph node dissection, the nomenclature established by the Japanese Rules for the Gastric Cancer Study[18] was used (*Tables 2* and *3*) and R_2 and R_3 dissections were the standard procedures performed. R_0–R_1 dissections were exceptional and confined to patients having microscopic cancer foci limited to the mucosa (*Table 4*).

The following clinical and pathological data of each patient were reviewed: age, sex, weight, tumour location, number of lymph nodes dissected, type of operation performed, number of metastatic nodes, microscopic stage, macroscopic stage, stomach wall involvement, total number of nodes dissected in each group, total number of metastatic nodes in each group and the postoperative mortality. The lymph nodes were histologically examined by haematoxylin and eosin stain, one section being made from each node for histological examination.

For statistical analysis the χ^2 test was used and statistical significance assumed when $P<0{\cdot}05$.

Table 1 *Operations performed*

Total gastrectomy + splenectomy and pancreas tail resection	85
Total gastrectomy	13
Subtotal gastrectomy	189
Proximal gastrectomy	5
Pancreaticoduodenectomy	8
Total	300

Table 2 *Regional lymph nodes of the stomach*

Group 1	Right paracardial	Group 9	Coeliac artery
Group 2	Left paracardial	Group 10	Splenic hilus
Group 3	Lesser curvature	Group 11	Splenic artery
Group 4	Greater curvature	Group 12	Hepatic pedicle
Group 5	Suprapyloric	Group 13	Retropancreatic
Group 6	Infrapyloric	Group 14	Mesenteric root
Group 7	Left gastric artery	Group 15	Middle colic artery
Group 8	Common hepatic artery	Group 16	Para-aortic

Table 3 *Lymph node groups around the regions of the stomach*

Site of tumour	R_1	R_2	R_3
Distal stomach	3, 4, 5, 6	1, 7, 8, 9	2, 10, 11, 12, 13, 14
Middle stomach	1, 3, 4, 5, 6	2, 7, 8, 9, 10, 11	12, 13, 14
Proximal stomach	1, 2, 3, 4	5, 6, 7, 8, 9, 10, 11	12, 13, 14
All stomach	1, 2, 3, 4, 5, 6	7, 8, 9, 10, 11	12, 13, 14

Table 4 *Relationship between postoperative mortality and level of nodes dissected*

	R_0	R_1	R_2	R_3
Mortality	0 (0%)	1 (3·2%)	4 (1·6%)	0 (0%)
Total	3	31	244	22

Table 5 *Relationship between postoperative mortality and number of nodes dissected*

	<30 nodes	≥30 to <60 nodes	≥60 nodes
Mortality	0 (0%)	3 (1·8%)	2 (3·1%)
Total	65	170	65

Table 6 *Relationship between number of nodes dissected and degree of node involvement in patients undergoing R_2 dissection*

	≥5 nodes with metastasis	≥12 nodes with metastasis	Total
<30 nodes dissected	6 (14%)	0 (0%)	43
≥30–<60 nodes dissected	26 (17·8%)	11 (7·5%)	146
≥60 nodes dissected	14 (25·5%)	4 (7·3%)	55

Results

The relationship between extent of lymph node dissection and postoperative mortality (defined as the patient's death within 30 days of the operation) was as follows: there was no significant difference between patients who underwent R_2 or R_3 dissections and those with less extensive dissection (*Table 4*). From the perspective of the total number of nodes dissected, there was also no statistically significant difference between the three groups (*Table 5*).

With regard to the relationship between the number of nodes dissected and the degree of node involvement, the differences did not reach statistical significance despite a relationship between the number of nodes dissected and the number of nodes involved (*Table 6*). Furthermore, if we analyse the number of nodes dissected in patients with more than 12 nodes involved, each one of these patients had more than 30 nodes dissected. In order to study patients in whom the same type of dissection was performed, only patients who underwent R_2 dissections were included in this part of the study.

A relationship between the number of nodes dissected and the proportion of patients with lymph node metastasis was observed (*Table 7*). If more nodes were dissected the proportion of patients with node involvement increased significantly ($P<0·05$). Patients who underwent lymph node dissections other than R_2 were excluded from this part of the study for the reasons mentioned above.

Microscopy revealed node involvement in 9·5 per cent of the patients who were not suspected of possessing it and who had been macroscopically catalogued N_0. Similarly, when the extent of node involvement was macroscopically evaluated among patients catalogued N_1 during operation, metastases were found in the n_2 group of nodes in 20·2 per cent of cases.

The percentage of metastatic involvement in every lymph node group dissected was analysed (*Tables 8*, *9* and *10*). Patients who had multiple tumours in more than one region of the stomach were excluded. In addition, when the tumour spread involved more than one portion of the stomach, the more involved portion was considered to be the primary location. When the tumour involved the distal portion of the stomach the nodes most frequently involved were those along both curvatures and around the pyloric region, nodes catalogued N_1 according to the General Rules for the Gastric Cancer Study[18]. The second most frequently involved nodes were around the left gastric artery and hepatic artery. When the tumour lay in the middle portion of the stomach, the most frequently involved nodes were those along both curvatures, the nodes around the pyloric region, and the nodes around the oesophagogastric junction. In this group of tumours it is important to point out that nodes along the splenic vessels and in the hilus of the spleen were involved in 10·2 per cent and 10·3 per cent of instances respectively (*Table 9*). In those tumours situated in the proximal stomach the nodes more commonly involved were those along the lesser curvature, around the oesophagogastric junction, and around the splenic vessels. Involvement was detected in 24 per cent of the nodes dissected. In this group of tumours it is also important to note the involvement of nodes around the left gastric artery and in the splenic hilus (*Table 10*).

Discussion

Early diagnosis followed by a prompt operation certainly has considerably improved the results of treatment of gastric

Table 7 *Relationship between number of nodes dissected and the proportion of patients with node involvement in patients undergoing R_2 dissection*

	No. patients with nodal involvement	Total no. of patients
<30 nodes dissected	13 (30·2%)	43
≥30 nodes dissected	95 (47·3%)*	201
≥60 nodes dissected	30 (54·5%)**	55
Total	108 (44·3%)	244

* $P<0·05$ in relation to the group of patients with <30 nodes dissected
** $P<0·05$ in relation to the group of patients with <30 nodes dissected

Table 8 *Node involvement in tumours located in the distal stomach*

Lymph node group	Percentage of metastatic involvement	Node catalogue
Group 4	32·4	N_1
Group 3	26·3	N_1
Group 5	20·0	N_1
Group 6	13·3	N_1
Group 7	13·3	N_2
Group 8	13·0	N_2
Group 1	6·0	N_2
Group 9	5·5	N_2
Group 12	2·7	N_3
Group 14	2·3	N_3
Group 13	1·8	N_3

Table 9 *Node involvement in tumours located in the mid-stomach*

Lymph node group	Percentage of metastatic involvement	Node catalogue
Group 3	27·2	N_1
Group 4	21·7	N_1
Group 5	13·3	N_1
Group 6	9·9	N_1
Group 1	8·8	N_1
Group 2	13·7	N_2
Group 10	10·3	N_2
Group 11	10·2	N_2
Group 7	9·5	N_2
Group 9	4·3	N_2
Group 8	2·1	N_2

Table 10 *Node involvement in tumours located in the proximal stomach*

Lymph node group	Percentage of metastatic involvement	Node catalogue
Group 3	42·2	N_1
Group 1	29·6	N_1
Group 2	21·0	N_1
Group 4	18·6	N_1
Group 11	24·0	N_2
Group 7	19·6	N_2
Group 10	9·2	N_2
Group 8	5·6	N_2
Group 9	5·2	N_2
Group 6	1·7	N_2

cancer[4,5,13]. But even in Japan, in spite of active endoscopy programmes and mass survey examination, the majority of the patients with gastric cancer have advanced disease. In 1960, Jinnai recommended extended lymph node dissection in order to improve the results of surgical treatment[19] and subsequently many surgeons began to use extended lymph node dissection. Many reports have supported this procedure[2,3,9–11]. However, in 1969 Gilbertsen[17] reported disappointing results from lymph node dissection in the surgery of gastric cancer. He found that extensive lymph node dissection led to a postoperative mortality rate of 25 per cent, and the 5-year survival rate fell from 12·8 to 8·8 per cent.

In the present study, a low rate of postoperative mortality was observed (1·7 per cent). Furthermore, postoperative mortality was not affected by the extent of dissection performed. When this relationship was studied according to the total number of nodes dissected, a slight difference between the group with more than 60 nodes dissected and the group with less than 60 nodes dissected was observed, but this difference did not reach statistical significance. One reason for this low postoperative mortality may be that the analysis was limited to patients who underwent curative resections, implying less advanced cancer and it should be stressed that early gastric cancer accounts for 30 per cent of the patients with gastric cancer in Japan[20]. The effect of the lymph node dissection on survival has been studied using control series from different time periods[2,3,12]. In all of these studies there has been an improved survival without adverse effects on postoperative mortality during the period in which extended dissection was employed. However, caution must still be exercised in drawing conclusions from retrospective studies in which results from two different periods of time are compared. Despite this proviso, the results obtained support the concept that lymph node dissection may have a role in the treatment of gastric cancer.

The present report has focused on the study of the efficacy of lymph node dissection, not in relation to the 5-year survival rate but in relation to the number of involved lymph nodes that could be left in place when the lymph node dissection is not employed. Within the types of resection studied it is possible to conclude that if a great number of nodes are dissected, more metastatic nodes may be extirpated and more patients with occult metastasis may be detected.

Another important point to consider is the risk involved in classifying nodal status on the basis of macroscopic features and in making decisions based on this evaluation. Some authors consider that intra-operative node biopsy may be useful[13]. Our assessment of the nodes most commonly involved in our resections of gastric cancer confirms the value of the division proposed by the Japanese Rules for the Gastric Cancer Study in which nodes are divided into three categories according to the primary location of the tumour (*Table 3*). Although a high percentage of the patients (40·3 per cent) had lesions catalogued as 'early', among the nodes dissected there were a considerable number of nodes involved, many of which would not normally be included in a standard gastrectomy. It is also important to underline the high incidence of involvement of the nodes along the splenic vessels and in the hilus of the spleen when the tumour is located in the upper stomach. This also applies to cases in which the tumour is located in an area other than the upper stomach, yet secondarily involves that region. Splenectomy in the treatment of gastric cancer is controversial because of the possible immunological role of the spleen[21–25]. However, complete dissection of the nodes in the hilus of the spleen and along the splenic vessels in patients with tumours located in the upper stomach means that splenectomy with pancreatic tail resection should be added to total gastrectomy in the majority of such patients.

We conclude that although early diagnosis is the best way of improving survival in patients with gastric cancer, routine lymph node dissection seems to have a role in the treatment. It allows extirpation of a greater number of metastatic nodes and the detection of more patients with such metastasis. Furthermore this procedure may be performed without affecting postoperative mortality rate.

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Surgical workshop

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Modified dissecting forceps for handling expanded PTFE arterial prostheses

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Arterial prostheses manufactured from expanded polytetrafluoroethylene (PTFE) are relatively stiff and even the thin-walled varieties have a tendency to invert after the PTFE graft has been trimmed to shape with a knife against a curved haemostat. In addition to this, problems can arise when attempting to evert the graft at the time of anastomosis to an artery. Previous authors[1] have suggested an alternative suturing technique to abolish this inversion of the graft edges but I have found that the handling of the graft can still present problems. In order to overcome these difficulties a modified pair of dissecting forceps have been designed.

The tips of a pair of forceps were altered to create a fine tooth with a concave surface on one shaft and an opposing convex pad on the other. When the prosthesis is grasped with the concave tip of these forceps on the luminal side the effect is to evert the graft and present the edge for suture placement (*Figure 1*). An additional modification involves covering the shafts of the forceps with silastic sleeves in order to allow the surgeon to hold sutures.

I do not find these forceps necessary or convenient for the whole anastomosis but they are useful intermittently when the graft is tending to invert. The forceps are, of course, also useful when using a more rigid Dacron® graft if handling is awkward.

Acknowledgements

I am grateful to W. L. Gore & Associates (UK) Limited for their help in manufacturing these forceps and to Ian Braby in particular for the photography and liaison.

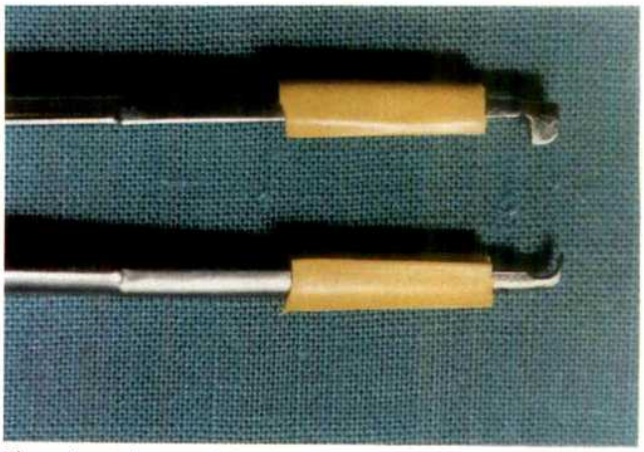

Figure 1 *A close-up of the forceps' tips showing the modification*

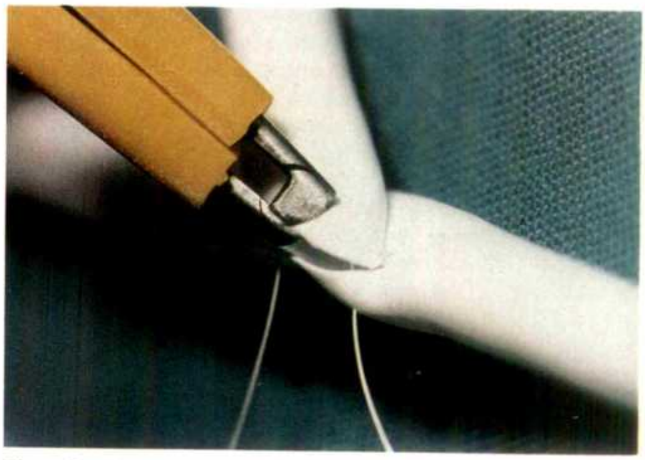

Figure 2 *The mode of action on a PTFE graft*

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Barrett's oesophagus: pH profile

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Twenty-four patients with a columnar-lined (Barrett's) oesophagus underwent oesophageal manometry and 24 h ambulatory oesophageal pH monitoring. The results were compared with 25 patients with oesophagitis studied in the same fashion. No significant difference in lower oesophageal sphincter pressure was demonstrated between the two groups. The Barrett's patients demonstrated significantly greater acid exposure in the distal oesophagus than oesophagitis patients. Clearance of refluxed acid was poorer in Barrett's patients than oesophagitis patients. Twelve of the Barrett's patients presented with complications of the condition, i.e. ulceration or stricture. No significant difference in acid exposure was demonstrated between Barrett's patients with or without complications. These results suggest that patients with columnar-lined (Barrett's) oesophagus have greater acid exposure than patients with oesophagitis. The development of complications of a Barrett's oesophagus may not be dependent on acid reflux alone.

Keywords: Barrett's oesophagus, acid reflux, oesophagitis, acid clearance

Barrett's oesophagus is generally accepted as being a metaplastic process involving replacement of squamous epithelium by columnar epithelium consequent upon gastro-oesophageal reflux[1]. The almost invariable association between Barrett's epithelium and reflux supports the view that the condition is acquired[2–5]. Severe reflux may exist in the absence of Barrett's epithelium and give rise to the changes of oesophagitis only. This observation led Iascone[6] to suggest that 'Barrett's oesophagus could be considered an end stage of reflux oesophagitis rather than an separate disease'. To examine this hypothesis the pH profiles of two separate groups of patients—one with Barrett's oesophagus and one with oesophagitis—have been assessed to determine the comparative degree of reflux between the two groups.

Patients and methods

During the period January 1984 and September 1986, 24 patients with reflux symptoms were documented as having Barrett's oesophagus. The diagnosis of Barrett's oesophagus was accepted when columnar epithelium was observed to extend more than 5 cm above the gastro-oesophageal junction at endoscopy and was confirmed on histology. During the same period, 25 patients were seen who had oesophagitis confirmed on endoscopy and biopsy which had failed to respond to medical therapy and who underwent anti-reflux surgery. These patients were used as a comparative group in assessing the reflux profiles of the patients with Barrett's oesophagus.

Oesophagitis was graded I–IV according to the endoscopic appearances[7]: grade I, distal erythema and mucosal friability; grade II, superficial necrosis and linear ulcerations; grade III, confluent or circumferential areas of deeper ulceration and erosion; grade IV, extensive mucosal necrosis and ulceration with stricture formation. Nine patients had either grade I or II oesophagitis, eight had grade III, and eight had stricture formation (grade IV).

Oesophageal manometry

Oesophageal manometry was performed on all patients using a triple-lumen polyvinyl catheter assembly with three side holes spaced 5 cm apart from the distal end of the catheter and located 120° radially to one another. The catheter assembly was perfused by a pneumohydraulic low compliance perfusion system and intraluminal pressure was transmitted via external transducers and recorded on a Devices multichannel pen recorder. The catheter assembly was introduced *per nares* in the fasting patients, passed into the stomach and withdrawn using a station pull-through technique until the high-pressure zone was located at the distal oesophagus. The lower oesophageal sphincter pressure was recorded as the difference between end-expiratory intragastric pressure and the maximal sphincter pressure at the respiratory reversal point[8]. The sphincter pressure taken was the mean of three pull-throughs.

Following identification of the high-pressure zone on manometry, the catheter assembly was withdrawn and an antimony-tipped pH electrode (Synectics) was positioned 5 cm above the high-pressure zone. Intra-oesophageal pH was monitored and recorded on a solid state Digitrapper and the study period was 24 h in all patients. The 24 h pH data were analysed using Synectics pH software and an Apple Computer. A reflux event was defined as a fall in the intra-oesophageal pH to 4 or less which lasted 5 s or longer. The data were analysed according to total number of reflux episodes, total time spent at pH 4 or less as a percentage of the study period and the total number of reflux events of 5 min or longer duration.

Statistical evaluation of the differences in pH scores and sphincter pressures between the two groups was by the Wilcoxon Rank Sum Test and Signed Rank Test for the analysis of non-parametric data.

There were 14 men and 10 women in the Barrett's oesophagus group with ages ranging from 34 to 80 years. The mean age was 65 years. There were 15 men and 10 women in the oesophagitis group with ages ranging from 23 to 73. The mean age in the oesophagitis group, 49 years, was significantly less than the Barrett's group, 65 years ($P < 0.05$, Student's t test unpaired data).

Endoscopy

In the Barrett's group ($n = 24$) eight patients presented with established stricture formation in the upper/mid-oesophagus with columnar epithelium distal to the stricture. In addition, one patient with an oesophageal stricture had an associated Barrett's ulcer in the columnar epithelium. Three patients presented with Barrett's ulcer in a columnar segment and one of these had three separate ulcers noted on successive endoscopies at 2 month intervals which had failed to heal on intensive medical therapy. Twelve patients had uncomplicated Barrett's oesophagus.

Extent of Barrett's epithelium

The extent of Barrett's epithelium, as measured endoscopically, ranged from 5 to 15 cm. The mean vertical extent of the columnar epithelium was 8 cm.

Barrett's epithelium: histological types

Specialized columnar epithelium. Eight patients demonstrated specialized columnar epithelium with features of intestinal mucosa—displaying crypts and a villiform surface with goblet cells.

Junctional-type epithelium. Six patients demonstrated junctional-type epithelium with rudimentary villi and a predominantly foveolar surface pattern. Goblet cells are not seen in this epithelial type.

0007-1323/87/090774-03$3.00

Gastric fundic-type. Four patients demonstrated this variety which resembles mucosa found in the body and fundus of the stomach.

In addition, four patients demonstrated features of both specialized and junctional mucosa on biopsy specimens and two patients had a combination of junctional and fundic types.

Results

The indices compared in the Barrett's group and the oesophagitis group are listed in *Table 1*.

Oesophageal manometry

There was no significant difference in lower oesophageal sphincter pressure between the Barrett's group and the oesophagitis group (median 15, range 3–25 mmHg *versus* median 17, range 8–28 mmHg).

Twenty-four hour pH scores

There was no significant difference (*Table 1*) in the total number of reflux episodes which occurred in the 24 h period between the Barrett's group (median 48, range 1–129) and the oesophagitis group (median 44, range 5–195).

The percentage time spent at pH 4 or less was significantly greater in the Barrett's group (median 32·9, range 1·0–75·2) than the oesophagitis group (median 11·0, range 1·0–40·2) ($P<0·01$, Wilcoxon Rank Sum Test).

The total number of reflux episodes which were greater than 5 min duration was significantly greater in the Barrett's group (median 11, range 0–25) than the oesophagitis group (median 6, range 0–11) ($P<0·05$, Wilcoxon Rank Sum Test).

Comparison of indices in the two Barrett's groups (Table 2, *Wilcoxon Signed Rank Test*). There was no significant difference in lower oesophageal sphincter pressures between the complicated Barrett's group (median 16, range 10–25 mmHg) and the uncomplicated Barrett's group (median 10, range 3–20 mmHg). There was no significant difference (*Table 2*) in number of reflux episodes (median 53, range 5–195 *versus* median 44, range 8–133), percentage time pH was less than 4 (median 30·3, range 6·4–75·2 *versus* median 32·3, range 2·8–73·8), or number of reflux episodes longer than 5 min duration (median 9, range 3–24 *versus* median 11, range 0–25).

Supine reflux: comparison of the two groups of Barrett's patients. There was no significant difference in percentage time spent at pH 4 in the supine position in the complicated (median 28, range 0·3–94·9) and uncomplicated Barrett's patients (median 32, range 0·8–74·8).

Comparison of indices in patients with oesophageal strictures (n = *8*) *and complicated* (n = *12*) *Barrett's groups* (Table 3). There was no significant difference in total number of reflux episodes, percentage time pH 4, or number of reflux events longer than 5 min duration between any of these groups.

Discussion

Few studies[6,9] have reported on combined manometry and 24 h pH studies in endoscopically and histologically proven Barrett's oesophagus. Iascone[6] demonstrated that acid exposure was greater in Barrett's patients than in an oesophagitis group in terms of percentage time pH<4, total number of episodes, longest reflux event and acid clearance, and claimed a linear relationship between extent of Barrett's epithelium and the level of reduction in lower oesophageal sphincter pressure and number of events longer than 5 min. Flook and Stoddard[9]

Table 1 *Comparison of patients with Barrett's oesophagus and patients with oesophagitis*

	Lower oesophageal sphincter pressure (median + range)	Total number of reflux episodes (median + range)	Percentage time pH < 4 (median + range)	Number of reflux episodes > 5 min (median + range)
Barrett's oesophagus ($n=24$)	15 mmHg (3–25 mmHg)	48 (1–129)	32·9 (1·0–75·2)	11 (0–25)
Oesophagitis ($n=25$)	17 mmHg (8–28 mmHg)	44 (5–195)	11·0** (1·0–40·2)	6* (0–11)

* $P<0·05$, ** $P<0·01$; Wilcoxon Rank Sum Test

Table 2 *Comparison of Barrett's patients with and without complications*

	Lower oesophageal sphincter pressure (median + range)	Total number of reflux episodes (median + range)	Percentage time pH < 4 (median + range)	Number of reflux episodes > 5 min (median + range)
Complicated Barrett's ($n=12$)	16 mmHg (10–25 mmHg)	53 (5–195)	30·3 (6·4–75·2)	9 (3–24)
Uncomplicated Barrett's ($n=12$)	10 mmHg (3–20 mmHg)	44 (8–133)	32·3 (2·8–73·8)	11 (0–25)
	n.s.*	n.s.*	n.s.†	n.s.†

n.s., not significant; * Wilcoxon Signed Rank Test; † Wilcoxon Rank Sum Test

Table 3 *Comparison of grade IV oesophagitis patients (oesophageal strictures) and patients with and without complications of Barrett's oesophagus*

	Total number of reflux episodes (median + range)	Percentage time pH < 4 (median + range)	Number of reflux episodes > 5 min (median + range)
Complicated group ($n=12$)	53 (5–195)	30·3 (6·4–75·2)	9 (3–24)
Uncomplicated group ($n=12$)	44 (8–133)	32·3 (2·8–73·8)	11 (0–25)
Benign oesophageal strictures ($n=8$)	48 (17–68)	27 (3·9–52·7)	7 (0–17)
	n.s.	n.s.	n.s.

n.s., not significant; Wilcoxon Rank Sum Test noted hypotensive lower oesophageal sphincter pressures in Barrett's patients and markedly increased acid reflux events with poor clearance when an oesophagitis group was used as control. Studies which have examined manometric findings in Barrett's oesophagus have conflicting reports on lower oesophageal sphincter pressure. Hypotensive sphincters have been reported by several authors. Wesdorp[10] reported 8 of 9 patients with Barrett's oesophagus who had no detectable sphincter pressure, while Heitmann[11] failed to identify a sphincter in 6 of 12 Barrett's patients. Using prolonged manometric recordings Patel[12] demonstrated sphincter pressures in Barrett's patients which were similar to levels found in oesophagitis patients studied in similar fashion. Since a considerable overlap in sphincter pressures occurs in normal controls and patients with reflux, it might be expected that some overlap exists between normals and patients with Barrett's oesophagus. Herlihy[13] has supported this concept by reporting that in the presence of oesophagitis a hypotensive sphincter is more likely to be present but in its absence normal pressures may occur—as he noted in half of his patients. This study has demonstrated considerable interindividual variations in lower oesophageal sphincter pressure levels in the group with Barrett's oesophagus and the oesophagitis group with considerable overlap between the groups. We have also failed to demonstrate an inverse relationship between reduction in lower oesophageal sphincter pressure and extent of Barrett's epithelium.

Although the mean age of the Barrett's group was greater than the oesophagitis group, this does not infer that development of the condition is consequent upon a prolonged period of symptomatic reflux. Patients may frequently present with complications of Barrett's oesophagus having been asymptomatic or having had only minimal symptoms. Similarly, prolonged symptoms of reflux often present with minimal mucosal damage.

The results of 24 h pH monitoring in this study have demonstrated that, as a group, patients with Barrett's oesophagus have longer acid exposure than patients with oesophagitis. Patients with severe oesophagitis who develop strictures, however, may have similar acid exposure to patients with Barrett's oesophagus but have no evidence of Barrett's epithelium. Interestingly, Spechler[14] has reported that Barrett's epithelium was documented in 11 of 25 patients with chronic peptic strictures who had no evidence at the time of initial diagnosis of Barrett's epithelium. Such a finding lends support to Iascone's contention that Barrett's oesophagus may be regarded as an end stage of reflux disease, although neither the degree nor duration of reflux alone appear to be responsible for the development of Barrett's epithelium since more than half of Spechler's chronic peptic strictures failed to show evidence of Barrett's epithelium and stricture patients demonstrated degrees of reflux similar to Barrett's patients in this study. It would appear from this study that the development of complications in Barrett's oesophagus, such as ulceration and stricture formation, is not solely dependent on acid exposure. Clearance of refluxed acid similarly failed to distinguish between complicated and uncomplicated Barrett's patients. It may be that a further mucosal injury in addition to acid is involved in the development of complications in this condition. Bile reflux has been implicated in the development of complications in Barrett's oesophagus by Bremner[15] and since significant bile acid concentrations may be detected in gastric juice of unaltered pH[16], further study in this area may elucidate the pathogenesis of complications in Barrett's oesophagus.

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Technical Data Overleaf

TECHNICAL DATA

DATA SHEET

PDS* (Polydioxanone) Sterilised Monofilament Synthetic Absorbable Suture

Presentation
PDS (Polydioxanone) Monofilament Synthetic Absorbable Suture is prepared from the polyester poly (p-dioxanone). The empirical molecular formula of the polymer is $(C_4H_6O_3)n$. PDS (Polydioxanone) sutures are coloured by adding either D & C blue No 6 (gauges metric 0.2 and 0.3, 10/0 and 9/0) or D & C violet No 2 (gauges metric 0.4 to 5.0, 8/0 to 2) during polymerisation. These sutures may also be manufactured undyed (clear).

PDS (Polydioxanone) sutures are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption.

Action
Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second, absorption rate or loss of mass.

Data obtained from implantation studies in rats show that, at two weeks post implantation, approximately 70% of the suture strength is retained whilst at four weeks the strength retention is approximately 50%. At eight weeks approximately 14% of the original strength remains. *This indicates a significantly longer period of wound support than previously available with an absorbable suture.*

The absorption or loss of mass is minimal until about the 90th post implantation day and is essentially complete within six months.

Uses
PDS (Polydioxanone) monofilament sutures are intended for use where an absorbable suture or ligature is indicated. They may have particular application where longer wound support is required. See strength retention data above.

Dosage and Administration
By implantation.

Contra-indications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

As with all monofilament synthetic sutures, care should be taken to ensure proper knot security.

Conjunctival, cuticular and vaginal epithelium sutures could cause localised irritation if left in place for longer than 10 days. Superficial placement of subcuticular sutures may also be associated with erythema and reaction during the course of absorption.

The safety and effectiveness of PDS (Polydioxanone) sutures in neural and cardiac tissue have not been established.

Pharmaceutical Precautions
Do not re-sterilise.

Legal Category P
Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Package Quantities
The gauge range initially available will be 0.2 metric (10/0) to 5 metric (2). Various lengths of material attached to non traumatic stainless steel needles are packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sale is 12 or 24 packs contained in a film wrapped drawer style carton.

Further Information
No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence Nos 0508/0011 (dyed); 0508/0012 (clear).
Br Pat No 1 540 053.

Date of preparation of Data Sheet—September 1982.
Revised 8/1986.

DATA SHEET

Coated VICRYL* (Polyglactin 910) Sterilised Braided Synthetic Absorbable Suture

Presentation
The basic VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$.

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided suture material with a mixture composed of a copolymer of glycolide and lactide and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

Coated VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Sutures may also be manufactured in the undyed form.

These sutures are relatively inert, nonantigenic, nonpyrogenic and elicit only a mild tissue reaction during absorption.

Action
Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second, absorption rate or loss of mass.

Subcutaneous tissue implantation studies of Coated VICRYL Suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

Uses
Coated VICRYL synthetic absorbable sutures are intended for use where an absorbable suture or ligature is indicated.

Dosage and Administration
By implantation

Contra-indications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 7 days and should be removed as indicated.

At the discretion of the surgeon, appropriate non-absorbable sutures may be used to provide additional wound support when coated VICRYL sutures are used in ophthalmic procedures.

The safety and effectiveness of Coated VICRYL (polyglactin 910) Sutures in neural tissue and in cardiovascular tissue have not been established.

Pharmaceutical Precautions
Do not re-sterilise.

Legal Category
Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Package Quantities
Various lengths of material packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sales is 12 packs contained in a film wrapped drawer style carton.

Further Information
No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence No 0508/0009
Br. Pat. No. 1583390

Date of Preparation of Data Sheet April 1981.
Revised 4/1987.

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Adhesion obstruction following Nissen fundoplication in children

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The incidence of postoperative adhesion intestinal obstruction among 156 children who had undergone Nissen fundoplication for intractable gastro-oesophageal reflux was determined. There were 18 episodes of obstruction in 16 patients (10·3 per cent). The mean interval between fundoplication and adhesion obstruction was 10 months (range 10 days–4 years). Additional procedures performed at the original laparotomy substantially increased the risk of developing obstruction. Re-laparotomy for adhesion obstruction was required by 21 per cent of patients who had a Ladd's procedure and 12 per cent who had appendicectomy. Presenting symptoms were not typical of intestinal obstruction because many of these children were unable to vomit. Only three did vomit but all had radiological appearances suggestive of small bowel obstruction. There were two deaths directly related to adhesion obstruction.

Keywords: Gastro-oesophageal reflux, Nissen fundoplication, adhesion obstruction

Nissen fundoplication is increasingly performed in children as surgical treatment for gastro-oesophageal reflux which has proven intractable to conservative methods of management[1,2], and when a complication, e.g. stricture formation[3], has developed. There have been two accounts of adhesion obstruction in children, following Nissen fundoplication, reporting an incidence of 5·1 per cent[4] and 6·2 per cent[5], and no associated mortality.

In our unit, this operation was frequently accompanied by an incidental appendicectomy or Ladd's procedure for malrotation i.e. unkinking the duodenal loop, widening the base of the small intestinal mesentery and placing the small bowel on the right side of the abdominal cavity and the large bowel on the left. A feeding gastrostomy was fashioned when the child had been experiencing major feeding problems—particularly in dysmorphic or severely retarded patients.

The sudden deaths, outside this hospital, of two of our patients as a result of adhesion obstruction, and the difficulty of diagnosing adhesion obstruction in a child who has been rendered incapable of vomiting by surgery, prompted us to review our patients for risk factors associated with the development of adhesion obstruction following Nissen fundoplication.

Patients and methods

Case notes of 156 children who had undergone Nissen fundoplication in the Professorial Surgical unit of the Hospital for Sick Children, Great Ormond Street between January 1980 and December 1985 were reviewed. All these patients were being followed up at regular intervals. Details of the anti-reflux procedure were recorded with particular note made of additional procedures performed. Episodes of adhesion obstruction requiring laparotomy were recorded and, where relevant, hospitals in which these patients were treated for adhesion obstruction were contacted and specific details obtained.

Results

Sixteen patients underwent laparotomy for relief of intestinal obstruction due to adhesion following Nissen fundoplication, an incidence of 10·3 per cent. In two children, two separate episodes of adhesion obstruction required laparotomy.

The age at Nissen fundoplication and interval between fundoplication and episode of adhesion obstruction is presented in *Table 1*. Mean age at the anti-reflux procedure was 2·4 years (range 0·25–7·10 years) and mean interval between Nissen and adhesion obstruction was 10 months (10 days–4·1 years). In 11 cases the episode of obstruction occurred within 4 months of the original procedure, while the remaining 5 episodes presented from 1 to 4 years postoperatively.

The presenting symptoms (*Table 2*) were not classical of intestinal obstruction. Only three children presented with bilious vomiting. The commonest presenting symptom was abdominal pain which occurred in 11 patients. The pain was frequently dramatic accompanied by drawing up of the knees and screaming. Passage of nasogastric tube resulted in aspiration of large volumes of bile-stained fluid in five patients.

Table 1 *Patients with adhesion obstruction following Nissen fundoplication*

Age at Nissen	Additional procedures	Interval to adhesion obstruction
90 days	Ladd's	2·07 years
150 days	Gastrostomy	42 days
4·75 years	Gastrostomy	54 days
7·10 years	Appendicectomy	1·30 years
4·40 years	Appendicectomy	35 days
4·90 years	Dense adhesions divided behind lesser curvature of stomach and liver	1·30 years
1·00 years	Appendicectomy Meckel's diverticulectomy	(1) 36 days (2) 120 days
1·14 years	Appendicectomy Ladd's	40 days
210 days	Appendicectomy Ladd's	4·07 years
5·17 years	Appendicectomy	2·60 years
300 days	Appendicectomy Ladd's	10 days
90 days	Ladd's	19 days
120 days	Ectopic pancreatic tissue excised from pylorus Pyloroplasty	90 days
330 days	Appendicectomy Ladd's	110 days
3·50 years	None	180 days
3·30 years	Gastrostomy Jejunostomy	(1) 24 days (2) 5 days

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Table 2 *Presenting symptoms*

Symptom	Number of children
Bilious vomiting	3
Abdominal distension	11
Obstipation	6
Retching	5
Abdominal pain	11

In all cases the plain abdominal X-rays revealed the typical features of small bowel obstruction with air–fluid levels and dilated loops of bowel.

Four patients were admitted to hospital in a poor general condition requiring vigorous resuscitative measures. There were two deaths in this group. One child died 40 days after fundoplication. She was dead on arrival at the local hospital and at necropsy infarction of a segment of small bowel by a thin peritoneal band was found. A second child died 3 months after the anti-reflux procedure. She was dehydrated and in circulatory collapse on admission to a district general hospital where after a brief period of resuscitation she underwent a laparotomy which revealed a fluid filled abdomen with an entero-enterogenous band in the mid-small intestine, and a grossly distended and perforated jejunum. She died 1 h postoperatively.

A third child died 7 months after lysis of an adhesion obstruction, from liver failure associated with prolonged parenteral nutrition for gastrointestinal disease unrelated to her surgical treatment.

Two children experienced two separate episodes of adhesion obstruction. In one child the first episode occurred 36 days after Nissen fundoplication and 12 cm of gangrenous ileum was resected. Four months later, a second episode of intestinal obstruction occurred and on this occasion multiple adhesions were found. The other child underwent a laparotomy for obstruction 24 days after the Nissen fundoplication. This revealed a band adhesion causing local necrosis while the rest of the small bowel was cyanosed and dusky. A further laparotomy was required 5 days later, when the anastomosis was found to be adherent and kinked in Morison's pouch.

In five children the diagnosis of intestinal obstruction was not considered in outside hospitals and they therefore received inappropriate treatment for the condition.

Additional procedures performed at laparotomy for the Nissen fundoplication are included in *Tables 1* and *3*. One patient (1·8 per cent) only of the 55 who had no additional intra-abdominal procedure performed with the Nissen fundoplication subsequently developed an adhesion obstruction. Appendicectomy was performed in 65 (41·7 per cent) of the children in this study and 8 (12·3 per cent) developed adhesion obstruction. Ladd's procedure for malrotation was performed in 18·6 per cent of patients and gave rise to the highest incidence of adhesive small bowel obstruction (20·7 per cent). There was also an increased risk in patients who had a concurrent Stamm gastrostomy; three of the seventeen (17·7 per cent) patients developed adhesion obstruction. The difference in incidence of adhesion obstruction in all groups of patients who had additional procedures performed at laparotomy compared with the patients who had Nissen fundoplication alone was statistically significant when examined by the χ^2 test ($P<0{\cdot}01$).

Discussion

The 10·3 per cent incidence of adhesion obstruction requiring laparotomy following Nissen fundoplication described in this paper is higher than previously reported[4,5]. The 21 per cent incidence in patients who additionally had a Ladd's procedure at the same laparotomy is also high in comparison with the 15 per cent incidence of adhesion obstruction following neonatal Ladd's procedure in this hospital[6]. It is, however, difficult to attribute the increased incidence in this group solely to the Ladd's procedure since many children had more than one additional procedure at Nissen fundoplication. If a malrotation is found at laparotomy it is mandatory to correct the abnormality by performing a Ladd's procedure[7]. It has been our experience that beyond the neonatal period, where malrotation is associated with a sliding hiatus hernia and significant gastro-oesophageal reflux, correction of the malrotation alone is insufficient to reverse the reflux symptoms. We would advocate concurrent Nissen fundoplication and Ladd's procedure in these patients. Similarly, although construction of a gastrostomy increased the risk of adhesion formation, the procedure was considered essential for feeding purposes in 17 patients. It is, however, salutory to note that the incidence of adhesion obstruction in the group in whom Nissen fundoplication alone was performed was only 1·8 per cent.

Table 3 *Additional procedures performed in 156 children undergoing Nissen fundoplication*

Procedure	Number of patients	Number with subsequent adhesion obstruction
Appendicectomy	65 (41·7)	8 (12·3)
Ladd's procedure	29 (18·6)	6 (20·7)
Gastrostomy	17 (10·9)	3 (17·7)
None	55 (35·3)	1 (1·8)

Numbers in parentheses are percentages

The performance of incidental appendicectomy resulted in a sixfold increase in adhesive small bowel obstruction and it is difficult to justify the continued addition of this procedure in children undergoing anti-reflux procedures, unless a Ladd's procedure is performed which then results in abnormal placement of the caecum.

The symptoms of intestinal obstruction following Nissen fundoplication are atypical since the fundal wrap renders the child unable to vomit. A partial wrap has been advocated to retain the ability of the child to vomit[8]. Abdominal X-rays in all our cases revealed air-filled levels and dilated loops of bowel, features pathognomonic of obstruction. Radiological investigation should, therefore, be undertaken early in a child who has had Nissen fundoplication presenting with abdominal pain or other features suggestive of obstruction.

The poor state of five patients on admission to hospital illustrates the rapid deterioration which can take place in a child with intestinal obstruction, and indicates the necessity for early referral. The death of one child in the immediate postoperative period also demonstrates that any child in whom adhesion obstruction is confirmed on plain abdominal X-ray should be adequately resuscitated before undergoing emergency laparotomy.

In all patients discharged from this unit following Nissen fundoplication, we emphasize in the discharge summary that there is a significant risk of developing adhesion obstruction which may present without bile stained vomiting but which needs early referral and intervention. The parents are also given written instructions concerning possible complications which may arise following fundoplication.

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Case report

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Total gastric gangrene complicating adult Bochdalek hernia

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Bochdalek hernia rarely presents in adult life; when it does it may be because complications have developed. Such a case is eported here.

Case report

A previously fit 25-year-old woman was admitted with a 4 h history of eft hypochondrial pain radiation to the back. It was precipitated by heavy lifting and a large meal. She had nausea but no vomiting. There was no history of previous illness or trauma.

On examination she looked anxious and in pain but not shocked. Her epigastrium was slightly tender. Chest X-ray was reported as clear *Figure 1*); the large gastric fluid level was thought to be due to elevation of the left hemidiaphragm. The leucocyte count (WBC) was 18·4 × 10⁹/l. She refused nasogastric tube suction and took her own discharge against advice 8 h later as the pain disappeared.

She was re-admitted 24 h later in shock and cyanosis with a pulse ate of 120 beats/min, BP 60/0 mmHg and a temperature of 35·4°C. The trachea was shifted to the right with absent breath sounds over the eft lung. The upper abdomen was tender and bowel sounds were absent. Chest X-ray showed left lung collapse and mediastinal shift with bowel gas and fluid levels filling the left hemithorax. WBC was 26·6 × 10⁹/l, erum urea concentration was 13·5 mmol/l and serum amylase 5000 units/l (normal level <300 units/l).

Laparotomy through an upper midline incision revealed free blood tained fluid. The spleen and gastric fundus were rotated anteriorly but emained below the diaphragm. The body and antrum of the stomach ogether with the omentum, transverse colon and splenic flexure, loops of the jejunum and the tail of the pancreas had herniated into the left pleural cavity through an opening, 10 × 5 cm, in the posterolateral part of the left hemidiaphragm. There was no hernial sac. The whole stomach was dilated and gangrenous with multiple perforations. The tail of the pancreas was oedematous but other structures were normal. Total gastrectomy and splenectomy with a Roux-en-Y anastomosis were performed. The defect was sutured with interrupted silk. The abdomen was closed and a chest drain was inserted. Postoperative wound infection resolved on conservative treatment and she was discharged ome. She remains well.

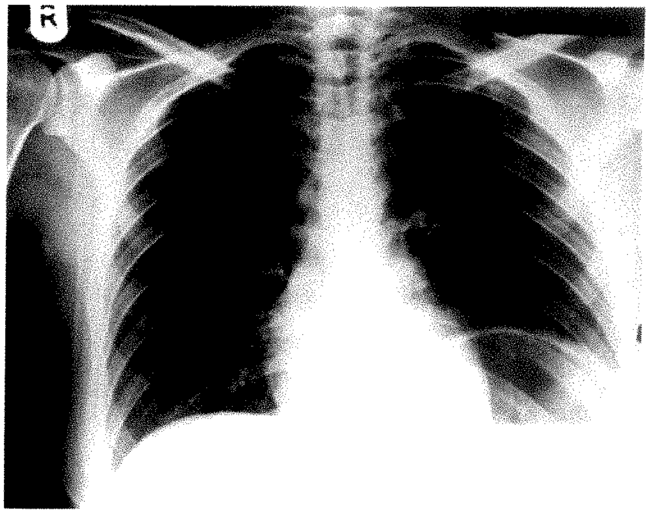

Figure 1 *Chest X-ray*

Discussion

Bochdalek hernia may rarely remain silent until it presents in adult life with gastrointestinal symptoms[1–4] in exactly the same fashion as herniae elsewhere. Although the stomach is frequently incarcerated in adult Bochdalek hernias[1–3], entire gastric gangrene has only been reported to complicate traumatic[4] and para-oesophageal[5] hernias. The deceptive regression of pain despite gangrene formation within such a short history stresses the need to be aware of the condition and the need for its immediate surgical correction.

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Outcome of surgery for Graves' disease re-examined

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The outcome of surgery for Graves' disease in terms of early and late morbidity was studied in 161 patients undergoing subtotal thyroidectomy in the 10-year period 1976–1985. Eighty of these patients had a minimum follow-up of 5 years. There was a low operative morbidity and a zero mortality. The weight of thyroid tissue preserved (in the range 5–10 g) influenced the prevalence of hypothyroidism at one year and at five years. There was a cumulative incidence of hypothyroidism which could not be reliably predicted from biochemical results during the first year. Over 60 per cent of patients with subclinical hypothyroidism at 4 months (63 per cent) or 1 year (70 per cent) did not subsequently need thyroxine replacement within 5 years. Patients remained at risk of developing recurrent toxicity indefinitely and the risk was significantly greater in patients with small goitres (<50 g). Our results may be improved by leaving larger remnants (9–10 g) in most patients and smaller remnants (2–4 g) in those with small glands in whom alternative treatment, which is to be preferred, is not acceptable. After subtotal thyroidectomy for Graves' disease lifelong follow-up is necessary.

Keywords: Graves' disease, subtotal thyroidectomy, postoperative thyroid failure, recurrent thyrotoxicosis, remnant weight

Of the treatment options for thyrotoxicosis (anti-thyroid drugs, radio-iodine and surgery) surgery remains appropriate for florid disease, during pregnancy, when medical management has failed, when there is a large goitre, when rapid control of the toxic process is desirable and when a patient is biased in favour of an operation. The objective of subtotal thyroidectomy is to make the patient euthyroid with a minimum incidence of either recurrent toxicity or thyroid failure. The availability of alternative non-operative methods of treatment makes it desirable that surgery carries a minimal risk and that the outcome is accurately defined.

The immediate results of subtotal thyroidectomy for Graves' disease are satisfactory in that postoperative morbidity is low[1–3] and mortality is now negligible. There is, however, considerable variation in the reported pattern of development of postoperative hypothyroidism and recurrent thyrotoxicosis. The incidence of thyroid failure reported ranges from 9 per cent[4] to 49 per cent[5] and recurrent toxicity from 1·5 per cent[5] to 15·6 per cent[6]. While these differences may be in part geographical[7], or due to the variable natural history of the disease and its response to surgery, there is enormous variability in the time of follow-up within and between studies which makes it difficult to draw conclusions on which to base clinical management.

The objectives of the present study were threefold: first to determine the morbidity in the total group of 161 patients; secondly, to determine the incidence and pattern of development of abnormal thyroid function in a sub-group of 80 patients with 5 year follow-up; finally, to define if possible the factors responsible for sub-optimal results.

Patients and methods

All patients undergoing surgery for Graves' disease in North-East Scotland and the Orkney and Shetland Isles are treated in a single unit under the care of one consultant. During the 10 years from 1976 to 1985, 161 patients were operated on for Graves' disease. One hundred and fifteen patients were identified from the Scottish Automated Follow Up Register (SAFUR) and a further 46 patients, not yet registered, from hospital records. Supplementary data were extracted from the case notes and stored and analysed on the Aberdeen University Honeywell 66/80 Computer.

Most patients were prepared with β-blocking drugs[8] rather than anti-thyroid drugs. Before 1983 propranolol was used but recently nadolol has been preferred, mainly because of the simpler dosage regime[9]. Patients who were euthyroid on antithyroid drugs at the time of referral for surgery continued on these drugs. Both groups of patients were given Lugol's iodine for 10 days pre-operatively.

A standard technique of subtotal thyroidectomy was used to preserve 6–8 g of thyroid tissue as estimated by visually judging the volume of the bilateral remnants. The strap muscles were not divided and the recurrent laryngeal nerves were always identified. Latterly, it became routine to identify and visibly preserve the parathyroid glands. Both inferior thyroid arteries were ligated in continuity. Two small bore suction drains were used and removed after 24–48 h. The platysma was closed with a continuous fine absorbable suture. Skin clips or staples were routinely removed on the first postoperative day.

The serum calcium level was checked on the first postoperative day and repeated at 48 h if low. An occlusive cough was accepted as evidence of intact recurrent laryngeal nerves.

Patients were seen for review at 1 month and at 3 monthly intervals for one year. Thereafter regular reviews were continued until thyroid function appeared to be stable. On each occasion the clinical thyroid status, serum thyroxine (T4) and (since 1980) serum thyrotrophin (TSH) levels were recorded. Once thyroid status was stable patients were entered on SAFUR for lifelong surveillance. Of the 161 patients, 80 had a minimum follow-up of 5 years.

Clinical thyroid failure was defined as clinical and biochemical evidence of hypothyroidism. Recurrent toxicity was defined as clinical and biochemical evidence of thyrotoxicosis. Subclinical failure was defined as clinical euthyroidism in the presence of either a low T4 (<70 nmol/l) and/or a high TSH (>10 units/l). The general policy was to avoid starting thyroxine replacement in the first year except if apparently unavoidable because of florid clinical features of failure.

Results

There were 127 females and 34 males with a median age of 29 years (age range 13–54 years).

Of 161 patients, 59 (37 per cent) were referred for surgery without prior medical treatment. The commonest reasons for this decision were the size of the goitre (54 per cent), relative youth (34 per cent) and the preference of the patient (25 per cent). One hundred and two patients (63 per cent) were referred for surgery after initial medical therapy. Relapse after completing one or more courses of drug therapy (55 per cent) and inadequate control of toxicity (30 per cent) were the main reasons for secondary surgical referral. The median time from surgical referral to operation was 4 weeks (range, 1–24 weeks).

The total weight of the thyroid gland was estimated by adding the weight of the resected portion of the gland to the surgeon's estimate of the weight of the remnant. The estimated total gland weight ranged from 22 to 160 g (median 60 g). The remnant weight ranged from 5 to 10 g (median 7 g) and the percentage of the gland resected from 65 to 96 per cent (median 85 per cent).

The most common early complication was transient biochemical hypocalcaemia (corrected serum calcium $<2{\cdot}2$ mmol/l) in 40/161 patients (25 per cent). Only three patients (2 per cent), however, had symptoms of hypocalcaemia and only one patient required replacement therapy because of apparent longterm hypoparathyroidism. There was no evidence of permanent damage to a recurrent laryngeal nerve (functionally or laryngoscopically) and no early postoperative problems requiring surgical intervention. Wound infection occurred in two (1 per cent) patients. There were no deaths.

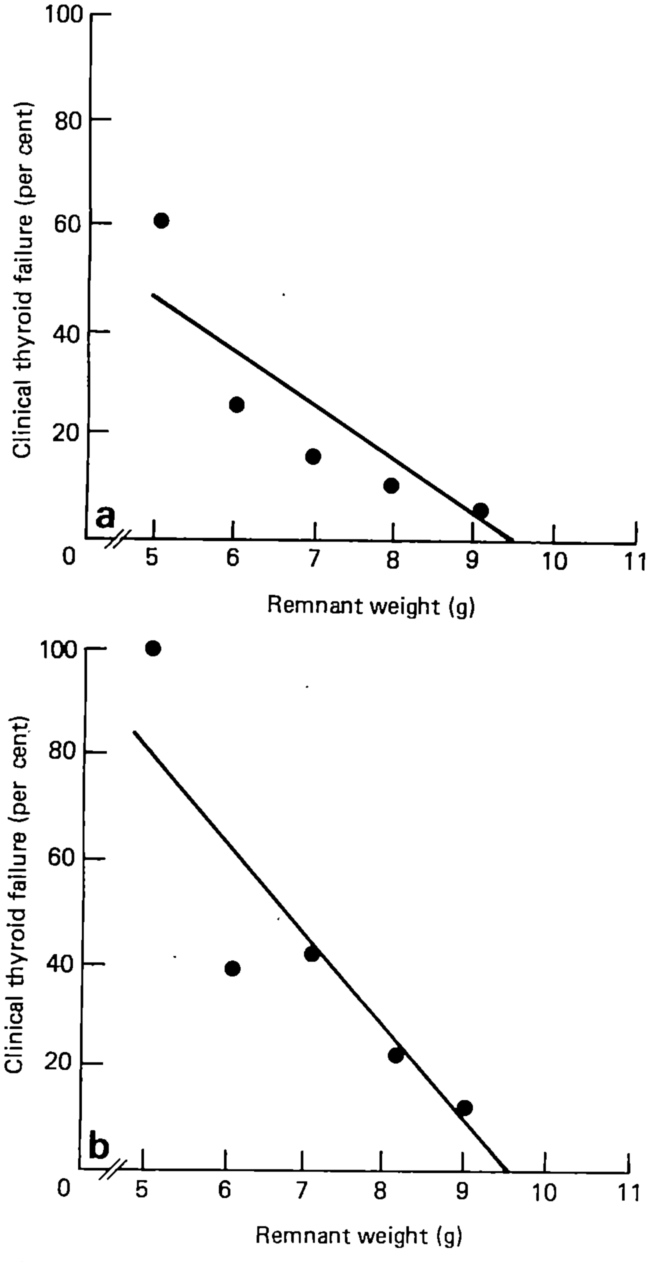

Figure 1 **a** *Relationship between remnant weight and postoperative clinical thyroid failure at 1 year in 144 patients* ($r=-0{\cdot}897$. **b** *Relationship between remnant weight and postoperative clinical thyroid failure at 5 years in 80 patients* ($r=-0{\cdot}915$)

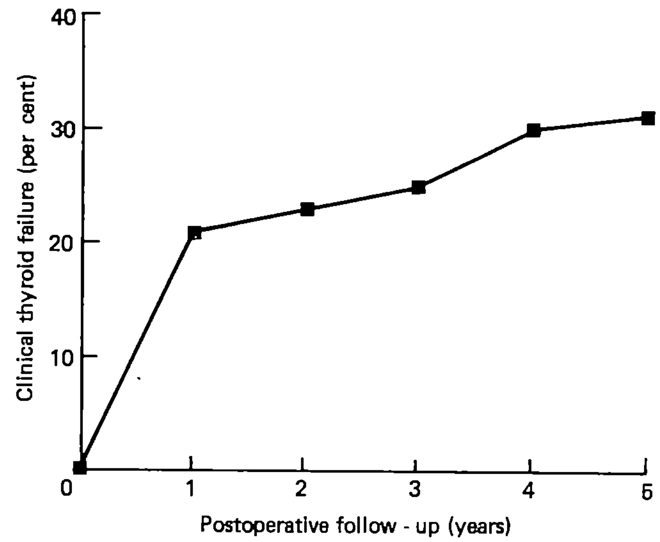

Figure 2 *Prevalence of postoperative clinical thyroid failure in 80 patients with a 5 year follow-up*

Postoperative stay ranged from 2 to 9 days (median 2·5, mode 2 days). The commonest cause of delay was the non-availability of a flight to the Orkney or Shetland Isles.

Of 144 patients with a 1 year follow-up, 22 patients (15 per cent) developed clinical thyroid failure and 1 patient (1 per cent) developed recurrent toxicity by the end of the first year. Eighty-five patients (59 per cent) were euthyroid and thirty (21 per cent) had subclinical failure. Biochemical values were unavailable in six cases. There was a strong inverse correlation between the remnant weight and the incidence of clinical thyroid failure at one year in these 144 patients ($r=-0{\cdot}0897$, *Figure 1a*).

In 80 patients with a 5 year follow-up, the prevalence of clinical thyroid failure increased from 17/80 (21 per cent) at 1 year to 25/80 (31 per cent) at five years (*Figure 2*). Of the eight patients who developed clinical thyroid failure after the first year, three were in subclinical failure and three had a normal T4 (TSH not available at one year). The status at one year is unknown in one patient and one patient was started on thyroxine, despite euthryoidism, at nine months because of pregnancy. This was stopped after delivery and the patient subsequently developed clinical thyroid failure. The high inverse relationship between remnant weight and the development of clinical thyroid failure was maintained at five years ($r=-0{\cdot}915$, *Figure 1b*).

There was a higher prevalence of clinical thyroid failure in patients over the age of 30 years (16/42, 38 per cent) compared to those under 30 years (9/38, 24 per cent) (*Figure 3*) but this was not statistically significant ($\chi^2=1{\cdot}2$, $P>0{\cdot}1$).

No relationship was found between thyroid failure and total gland weight or percentage of gland resected. There was a higher prevalence of failure at five years in the patients with a gland weight <50 g (34 per cent) compared to those of larger gland size (29 per cent). This is explained by a tendency to leave a smaller remnant in patients with small goitres (remnant weight <8 g in 63 per cent of patients with glands <50 g, and <8 g in 41 per cent of those with a gland weight >50 g).

A relationship was not demonstrable between clinical thyroid failure at five years and sex, auto-antibody status, preparation for surgery, previous medical treatment, or initial serum thyroxine level. Any possible relationship between thyroid failure and the subjective histological degree of lymphatic infiltration of the gland was not examined, although this has been implicated as a possible relevant factor[3,10].

Sixty-three per cent of patients (17/27) in subclinical failure at 4 months and 70 per cent of patients (7/10) in subclinical

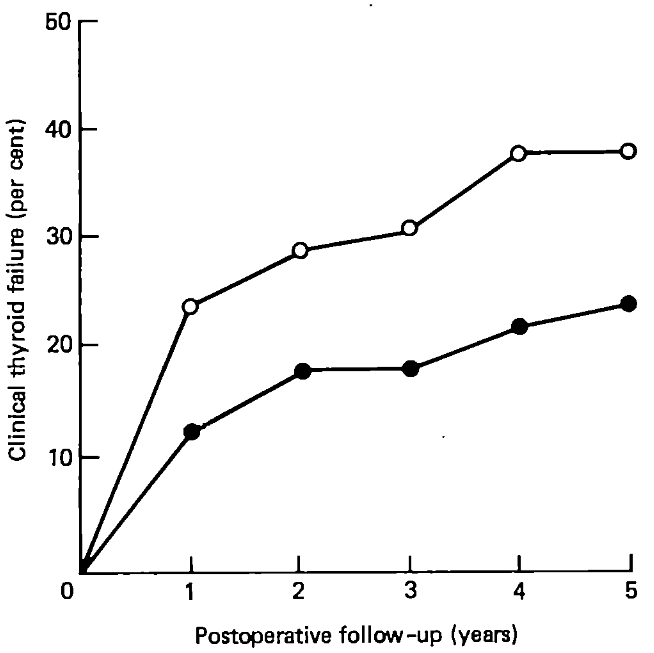

Figure 3 *Relationship between age and postoperative clinical thyroid failure in 80 patients (○ >30 years, ● ≤30 years) with a 5 year follow-up*

failure at 1 year did not subsequently require treatment for thyroid failure. At 1 year, of the 27 patients with subclinical failure at 4 months, 7 had developed clinical thyroid failure, 10 were clinically and biochemically euthyroid and 10 were still in subclinical failure. Of these ten in subclinical failure at the end of 1 year, three had failed by 5 years, four were clinically and biochemically euthyroid and three were still in subclinical failure (all with a normal serum T4 level but a raised TSH). Four per cent (1/27) of those euthyroid at 4 months and 6 per cent (3/47) of those euthyroid at 1 year, later developed clinical thyroid failure. No patient with clinical thyroid failure at 4 months or later reverted to euthyroidism.

During the first five postoperative years, 6/80 patients (7·5 per cent) developed recurrent toxicity at a rate of approximately one patient per annum. The small numbers did not permit calculation of correlation coefficients but recurrent toxicity was significantly more common when the gland weight was <50 g (5/34, 15 per cent) than when the weight was >50 g (1/45, 2 per cent) ($\chi^2 = 4{\cdot}2$, $P < 0{\cdot}05$). There was no demonstrable relationship to remnant weight. Recurrent toxicity was twice as common in patients aged over 30 years (4/42, 10 per cent) than in patients aged 30 years or under (2/38, 5 per cent). Two of twenty men (10 per cent) and 4/60 women (7 per cent) developed recurrent toxicity.

Discussion

This study confirms some of the attractions of surgery in the treatment of Graves' disease: morbidity was very low and mortality was zero. Management is expeditious especially when preparation is with β-blocking drugs, with a median time from referral to operation of 4 weeks. Hospital stay is short, with a median postoperative stay of 2·5 days. The disadvantages lie in the uncertainty of the outcome in relation to cure and subsequent thyroid failure as well as in the time elapsed between operation and definition of ultimate thyroid function. In the group of 80 patients followed up for a minimum of 5 years 96 per cent of those clinically and biochemically euthyroid at 4 months and 94 per cent of those euthyroid at 1 year maintained satisfactory thyroid function. The prevalence of clinical thyroid failure increased from 21 to 31 per cent between the first and fifth years. This is in contrast to previous reports from this and other centres stating that thyroid failure rarely develops after the first year[5,11,12,13]. Progressive thyroid failure over a number of years has been reported[14,15], but Michie[8] considered that this reflected failure to diagnose cases developing in the first year. In 1983 Hedley[16] suggested that while the majority of patients who develop thyroid failure do so in the early postoperative period, there remains a number of euthyroid patients who will become hypothyroid in the future at the rate of about 1 per cent per annum. It is possible that the differences between the results of this study and previous reports from the North-East of Scotland[5,8,16] reflect changes in management between 1972 and 1976. Prompted by the high rate of thyroid failure reported in 1972 (49 per cent)[5] it became policy by 1976 to leave a larger gland remnant (6–8 g). There was also a change in the selection criteria for surgery. Between 1965 and 1969 the mean annual number of patients undergoing subtotal thyroidectomy for all forms of thyrotoxicosis[5] was 56. Currently a mean of 16 patients are operated on for Graves' disease annually. In addition, we have avoided starting lifelong thyroxine replacement during the first year unless there is clinical evidence of hypothroidism.

The incidence of postoperative hypothyroidism has previously been overestimated because of failure to recognize that early hypothyroidism, both biochemical and clinical, may be temporary. Toft[17,18] argued that no patient should be started on thyroxine before 6 months, because many patients return to biochemical and clinical normality within that time after a period of mild hypothyroidism. He also reported that early measurement of TSH revealed two groups of patients: those with a normal TSH at 3 months having a lesser chance of developing thyroid failure subsequently than those with an elevated TSH.

From our data for 80 patients with a 5 year follow-up the majority of patients with evidence of subclinical failure (low T4 and/or high TSH) at either 4 months (70 per cent) or 1 year (63 per cent) did not subsequently require replacement thyroxine. Thus if all patients in subclinical failure, including those with a low serum T4, are started on thyroxine a number of patients are treated unnecessarily. However, every patient who was found to be in clinical failure (confirmed biochemically) at 4 months or later was ultimately started on thyroxine and clinical failure at or after 4 months therefore appears to be a definite indication for replacement therapy. It has to be admitted, however, that having had to start thyroxine with reluctance during the first year for florid hypothyroidism, we have not subsequently attempted to wean such patients off replacement.

We are unable to predict late failure from serum T4 and TSH levels in the first year but a high risk group can be identified: those patients with subclinical failure at 4 months have a nine-fold greater chance of later failure and those at one year have a five-fold greater chance than those who are euthyroid at these times. The majority of both groups, however, become euthyroid.

Remnant size has been claimed to be a determinant of the risk of thyroid failure[5,19], a small remnant resulting in an increased risk of hypothyroidism but others disagree[13,20]. Michie and Hedley[5,8,19] demonstrated a curvilinear relationship in the range 1–9 g, although the follow-up period was not defined. Makiuchi[13] failed to demonstrate a relationship between remnant weight and thyroid failure, but did not differentiate weights in the range 1–10 g. In the present study there was a strong inverse relationship between thyroid failure and remnant weight in the range 5–10 g at both 1 and 5 years. Although we acknowledge that estimates of remnant weight are neither accurate nor likely to be comparable between studies[19], remnant weight or size is a parameter that can be readily modified and recorded. Estimates within one surgical unit are sufficiently reproducible that a relationship to later thyroid failure has been established.

A relationship was not found between the initial total gland weight or the percentage of the gland resected and the development of hypothyroidism. The slightly higher incidence of failure in those with gland weight <50 g can be explained by a tendency to leave a smaller remnant in patients with a smaller gland.

There was an increased risk of thyroid failure in patients aged over 30 years at the time of surgery (38 per cent) compared with those under 30 years (24 per cent). This is in agreement with Thjodleifsson[21] but contrary to Michie's earlier findings[5] from this centre.

The pattern of recurrent thyrotoxicosis is in agreement with the observations of Hedley[22] and Makiuchi[13] that the number of patients with recurrent toxicity increases steadily over the years. The small number of patients (7·5 per cent) developing recurrent toxicity makes it difficult to determine any predisposing factors as in other reports. While it is generally accepted[10] that an increase in remnant weight will result in an increased incidence of recurrent thyrotoxicosis, there is a paucity of evidence to support (or refute) this. Makiuchi[13] demonstrated clearly that remnant size was important at weights over 10 g but did not distinguish between weights in the range 1–10 g. Tweedle in a prospective study[20] found no difference in the incidence of recurrent toxicity in the range 6–12 ml. Weights over 10 g were avoided in the present study and we were unable to relate recurrent toxicity to remnant weight in the range 5–10 g. However, the lower prevalence of recurrence (1·5 per cent) reported from Aberdeen[5] when the aim was to leave a smaller remnant weight is suggestive of a relationship between remnant size and recurrent toxicity. A significant relationship was observed between a low total gland weight and recurrent toxicity ($P < 0{\cdot}05$). Hedley[22] postulated that patients developing recurrent toxicity belong to a separate sub-population in whom the continuing presence of thyroid stimulating immunoglobulins is more common.

The evidence presented here with regard to outcome after operation for Graves' disease relates to the North-East of Scotland and may not be wholly applicable elsewhere. Thjodleifsson[21], in a comparative study between Iceland and Aberdeen with identical surgical protocol, reported that in Iceland, an area with a high dietary iodine level, the prevalence of postoperative clinical thyroid failure was 1/5 of that in the North-East of Scotland (an area of much lower dietary iodine). The prevalence of recurrent toxicity was 5 times greater in Iceland. The two populations also differed with regard to antibody status, the incidence of positive thyroid autoantibodies being significantly higher in Aberdeen.

In conclusion, the optimum remnant weight for our patients with gland weights greater than 50 g appears to be 9–10 g, which might be expected to reduce the risk of failure. Patients with a small gland (<50 g) are at higher risk of recurrent toxicity after operation and in the future alternative treatment will be recommended. If operation is undertaken then a remnant weight of 2–4 g will be the aim, accepting that there will be a high risk of thyroid failure in this group of patients. We admit that the logic of such a policy depends on a relationship between remnant size and recurrence and that the evidence for such a relationship is weak. However, the alternative of a controlled comparison between small and large remnants in patients with small glands is impractical because of the small number of patients available for study.

The continuing development of thyroid failure and recurrent toxicity makes indefinite follow-up mandatory.

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Conservative management of bleeding duodenal ulcer without a visible vessel: prospective randomized trial

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Between January 1983 and December 1985, 305 patients were admitted to our hospital because of bleeding duodenal ulcer. A subgroup of 69 patients aged 50 or above in whom emergency endoscopy showed non-arterial bleeding or signs of recent haemorrhage without a visible vessel entered a prospective therapeutic trial. The patients were randomized to receive either (1) early surgery, implying immediate operation, or (2) expectant management, with surgery reserved only for patients with further haemorrhage. The two groups were homogeneous with respect to age, sex, prior ingestion of ulcerogenic drugs, mode of bleeding, admission haematocrit, number with hypovolaemic shock and number with active bleeding on initial endoscopy. Overall mortality was 8·6 per cent. Mortality in patients submitted to early surgery was five times higher than that in those allocated to expectant therapy (14·7 per cent versus *2·9 per cent; risk ratio 5·07). The results suggest that expectant management is advisable in patients with bleeding duodenal ulcer not bleeding massively and in whom endoscopy does not disclose spurting arterial bleeding or a visible vessel.*

Keywords: Duodenal ulcer, upper gastrointestinal bleeding

In spite of advances in surgical technique and the availability of intensive care units, the mortality of upper gastrointestinal bleeding due to duodenal ulcer in elderly patients is still high[1,2]. Recurrent haemorrhage after hospital admission has been considered the most important predictor of outcome[3], and some authors have recommended an aggressive surgical approach to prevent deaths related to recurrent bleeding[4–6]. In contrast, others have advised expectant management, arguing that early surgery before bleeding has recurred would lead to many unnecessary operations with some operative deaths in patients in whom the bleeding episode would have been self-limited[7,8]. However, all of the cited studies were retrospective and in them the endoscopic appearance of the bleeding lesion was not considered, whereas it is now well known that this factor has prognostic value. Thus, the endoscopic observation of arterial bleeding or a visible vessel is associated with a high probability of relapsing haemorrhage (between 50 and 100 per cent)[9–11], justifying an aggressive approach in this situation. On the other hand, the likelihood of recurrent bleeding is practically nil in the absence of endoscopic signs of recent haemorrhage and an expectant attitude is advisable in these cases[10]. The published results of the only prospective study comparing expectant management with early surgery in bleeding peptic ulcer showed that early operation led to a significant reduction in the mortality of patients aged over 60 years, but only in those with gastric ulcer[2].

The aim of the present randomized, prospective study was to compare the results of early surgical therapy and expectant management in patients aged over 50 years with bleeding duodenal ulcer in whom endoscopy revealed active non-arterial bleeding or signs of recent haemorrhage in the absence of a visible vessel.

Patients and methods

Between January 1983 and December 1985, 305 patients with gastrointestinal bleeding due to duodenal ulcer were admitted to our hospital. Emergency endoscopy was carried out within 6 h of admission in all patients by personnel with experience in urgent endoscopy for upper gastrointestinal bleeding.

A duodenal ulcer was felt to be the site of bleeding when endoscopy revealed active haemorrhage, a visible vessel, or an adherent blood clot, or when the ulcer showed no signs of recent bleeding but there was blood in the stomach in the absence of other potentially bleeding lesions. A visible vessel was considered to exist when arterial bleeding (jet) or a red-bluish mass protruding from the ulcer base was observed, regardless of whether there was active bleeding or other signs of recent haemorrhage.

Emergency endoscopy demonstrated arterial bleeding or a visible vessel in 62 (20·3 per cent) patients, who were excluded from the trial and underwent early surgical intervention or transendoscopic therapy. Likewise 94 (30·8 per cent) patients with a duodenal ulcer not showing endoscopic signs of recent haemorrhage were excluded and assigned to expectant management because of their low probability of recurrent bleeding. Of the remaining 149 (49 per cent) patients with endoscopic evidence of recent haemorrhage other than a visible vessel, 70 aged under 50 years were excluded, as well as 10 aged over 50 years with a high individual operative risk because of the presence of two or more of the following factors: respiratory, cardiac or renal failure, recent myocardial infarction, decompensated diabetes mellitus, prolonged steroid treatment or chronic liver disease. Thus, 69 patients aged over 50 years without contra-indication to surgery in whom endoscopy revealed active non-arterial bleeding or evidence of recent haemorrhage from a duodenal ulcer without a visible vessel entered the trial.

After obtaining full informed consent, the patients were randomized using a random number table into two therapeutic groups: (1) early surgery or (2) expectant management.

All patients were admitted to an intensive care unit, where they remained for at least 72 h and received the usual resuscitation measures including blood transfusion as appropriate. Patients in the early surgical group were operated on within 4 h of admission by the on-call surgeon. Suture of the bleeding lesion plus truncal vagotomy and pyloroplasty were performed in all cases. Patients allocated to expectant management were treated with intravenous cimetidine (1200 mg/day) and liquid antacids (aluminium hydroxide and magnesium hydroxide; 30 ml/h through a nasogastric tube). Surgical therapy was undertaken in these patients only when bleeding persisted or recurred.

The severity of gastrointestinal bleeding was assessed by hourly measurement of the peripheral pulse, blood pressure, central venous pressure, urine output and nasogastric aspirate.

Table 1 *Comparison of demographic, clinical and endoscopic features in patients with bleeding duodenal ulcer submitted to two different therapeutic approaches*

	Early surgery	Expectant management	P
Age (years ± s.d.)	66·4 ± 11·1	65·1 ± 10·5	n.s.
Sex (men/women)	22/13	28/6	n.s.
Prior ulcerogenic drugs, *n*	19 (55%)	15 (44%)	n.s.
Admission haematocrit (± s.d.)	28·6 ± 8·3	31·7 ± 7	n.s.
Bleeding presenting as haematemesis, *n*	12 (35%)	11 (32%)	n.s.
Patients with shock, *n*	4 (12%)	3 (9%)	n.s.
Active bleeding seen at endoscopy, *n*	13 (38%)	11 (32%)	n.s.

n.s., not significant

Table 2 *Mortality in two therapeutic groups of patients with bleeding duodenal ulcer*

	Number of patients	Operations	Surgical mortality	Overall mortality	P
Early surgery	34	34	5	5 (14·7%)	n.s.
Conservative management	34	11 (32%)	1 (9%)	1 (2·9%)	

n.s., not significant

The haemorrhage was defined as persistent when the aspirated nasogastric contents remained blood-tinged for more than 48 h or transfusion requirements exceeded 6 units of blood. A recurrence was defined as either the presence of bloody gastric contents following a period of at least 12 h of clear aspirates, or as the occurrence of recent melaena requiring blood transfusion.

The end-point of the study was the evaluation of mortality related to the bleeding episode and occurring during the initial hospital admission. The statistical analysis was made using the Student's *t* test for comparison of means and 2 × 2 contingency tables with Yates' correction for the evaluation of qualitative variables. In addition, to determine the clinical significance of any differences between the two treatment groups, the 'relative risk' or 'risk ratio' was estimated as a proportionality index of mortality.

Results

Of the 69 patients entering the study, 50 were men and 19 women. Their ages ranged from 51 to 88 years, with a mean of 65·8 years (s.d. ± 10·5). Forty-seven (68 per cent) patients were over 60 years of age.

Thirty-five patients were allocated to receive early surgery and 34 patients were allocated to medical therapy. One patient from the first group was excluded from the trial after randomization because he refused surgery after having given his consent to be randomized. This patient had no further bleeding and his clinical course was uneventful.

The two groups of patients were homogeneous as regards age, sex, presence of underlying diseases, severity of bleeding and endoscopic findings (*Table 1*).

Overall mortality was 6/69 or 8·6 per cent (95 per cent confidence limits, 3·3–18·0 per cent). Five out of thirty-four (14·7 per cent; 95 per cent confidence limits, 5·0–31·1 per cent) patients from the group receiving early surgical therapy died, whereas only one out of thirty-four (2·9 per cent; 95 per cent confidence limits, 0·1–15·3 per cent) patients died in the group allocated to expectant medical treatment (risk ratio, 5·07) ($\chi^2 = 3{\cdot}23$; $0{\cdot}05 < P < 0{\cdot}1$) (*Table 2*).

The causes of death in the surgical group were: recurrent bleeding after surgery (1), hepatic failure (1), and respiratory complications (3). In the conservative treatment group, 23 (68 per cent) patients had no further bleeding, while 11 (32 per cent) patients had recurrent haemorrhage and had to be operated on. The only death in this group was due to postoperative cardiac complications.

Discussion

Until recently, the indication for early operation in bleeding peptic ulcer was established on the basis of existence of associated diseases, and the features of the haemorrhage itself, such as size of bleed, persistence or relapse[4–6]. All authors agree that massive bleeding deserves emergency surgery[12,13]. On the other hand, the mortality of non-massive bleeding is very low among young patients, which is why early surgery is not usually advised in this situation. The studies published to date comparing conservative management with early surgery in older patients are for the most part retrospective. In a retrospective study carried out in our unit 7 years ago the early surgical approach was associated with a significant reduction in mortality when compared with expectant management in patients aged over 50 years with non-massive bleeding due to duodenal ulcer[14]. However, as previously discussed, the endoscopic appearance of the bleeding lesion has prognostic value, and this feature was not usually considered in former studies.

Once patients with massive bleeding, visible vessels and arterial bleeding are excluded, there is little evidence to support the contention that an aggressive approach with early surgery might be more effective than a conservative attitude in older patients in whom endoscopy reveals active non-arterial bleeding or signs of recent haemorrhage. The results of our study in patients belonging to this particular group demonstrated that a systematic approach with early surgical treatment carries a mortality five times higher than that of expectant management with surgery reserved for patients who suffer further bleeding. The worse outcome in patients treated with early operation has a 90–95 per cent probability of not being due to chance alone and, besides its statistical significance, has sufficient clinical value to discourage an aggressive approach which offers no advantages over a conservative attitude.

Although different designs in published studies make comparisons difficult, it is likely that the beneficial effects of early surgical therapy found by some authors depend on the inclusion in the surgical groups of patients with arterial haemorrhage or a visible vessel, who account for 18–48 per cent of all patients with bleeding peptic ulcer[9–11,15].

The prospective study of Morris *et al.*[2] comparing the benefits of early *versus* delayed operation in patients with bleeding gastroduodenal ulcer indicated that an aggressive surgical approach reduced mortality in patients aged over 60 years. However, careful scrutiny of the methodology in this study shows that early surgery was indicated on the basis of criteria which included, besides a visible vessel, the persistence or recurrence of bleeding. Because the latter were the criteria that established a surgical indication in the patients submitted to expectant management in our study, we believe that our results not only do not contradict those of Morris *et al.*[2], but are even complementary, supporting the notion that early surgery should not be undertaken before bleeding has recurred but is mandatory once that has taken place.

In conclusion, the results of the present study suggest that a conservative approach is advisable in patients with duodenal ulcer who do not bleed massively and in whom endoscopy does not disclose spurting arterial bleeding or a visible vessel.

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Late results of mesocaval interposition shunting for bleeding oesophageal varices

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Survival, encephalopathy and shunt patency were studied in 64 consecutive patients who underwent mesocaval shunting with a wide-calibre Dacron® prosthesis. Half of the patients were operated as emergency cases. Operative blood loss in patients who had emergency procedures was significantly higher than during elective operations. Overall, 30-day mortality was 27 per cent. Survival was 61 per cent after 1 year and 39 per cent after 5 years. Serious encephalopathy requiring hospital admission occurred in 5 patients (11 per cent of patients surviving more than 1 month). Shunt patency was assessed by scintisplenoportography and ultrasonography. Cumulative shunt occlusion rate was 16 per cent after 1 year, 33 per cent after 5 years and 52 per cent after 8 years of follow-up. Out of 17 patients with an occluded shunt, 9 had persistent or recurrent bleeding, while 3 patients had recurrent bleeding despite a patent shunt. We conclude that the mesocaval Dacron interposition shunt should not be recommended as the procedure of first choice for portosystemic shunting.

Keywords: Mesocaval shunt, portal hypertension, liver cirrhosis, bleeding oesophageal varices, thrombosis, scintisplenoportography, ultrasonography

In 1972 Drapanas propagated the mesocaval interposition shunt, with the use of a wide-calibre Dacron* prosthesis, for the treatment of bleeding oesophageal or gastric varices[1]. He stated that 'synthetic grafts placed between the superior mesenteric vein and inferior vena cava remain patent for a long period, offer the potential for continued perfusion of the liver by an intact portal flow from the upper abdominal viscera, and are accompanied by an extremely low incidence of hepatic encephalopathy'. Drapanas' successor, Dowling, reached the same conclusions in 1979[2].

After the first reports with favourable results from the mesocaval interposition shunt, this procedure became the operation of choice from 1974 to 1982 for patients with bleeding from oesophageal or gastric varices who were admitted to this hospital. In this communication we report the long-term results of mesocaval shunting with emphasis on survival, encephalopathy and shunt patency.

Patients and methods

From July 1974 to December 1982, 64 consecutive patients underwent a mesocaval interposition shunt. There were 37 men and 27 women patients with a mean age of 53 years (range 21–75 years). All patients had experienced at least one episode of endoscopically proven major bleeding from oesophageal or gastric varices or were actively bleeding from varices at the time of admission. The severity of liver disease, according to the Child–Campbell classification[3], was Child A in 27 patients (42 per cent), Child B in 32 patients (50 per cent) and Child C in 5 patients (8 per cent). Aetiology of the chronic liver disease is shown in *Figure 1*. Of the patient population 48 per cent had alcoholic liver disease. Angiography was part of the pre-operative workup. Non-visualization of the superior mesenteric vein was considered to be a contra-indication for mesocaval shunting. This was found in nine patients admitted in the same period; a portacaval or splenorenal shunt was constructed in those patients.

If the patient was bleeding at the time of admission to the hospital, initial treatment consisted of intravenous administration of vasopressin and the insertion of a Sengstaken–Blakemore tube. If the bleeding persisted in spite of these measures an emergency mesocaval shunt was carried out. Surgery was also performed if the bleeding recurred after deflation of the Sengstaken balloon, 12–24 h after insertion. Thirty-two patients (50 per cent) were operated upon while they were (re)bleeding either as a failure of the initial treatment or after deflation of the Sengstaken–Blakemore tube. In the other half of the patients the operation was performed after recovery from the bleeding, either within 48 h of admission (24 patients, 38 per cent) or after several days or weeks as an elective procedure (8 patients, 12 per cent).

The operation was performed as described by Drapanas[1], using a 20 or 22 mm diameter Dacron prosthesis, but modified so that: firstly one part of the prosthesis was anastomosed to the inferior vena cava, then another piece of Dacron prosthesis was anastomosed to the superior mesenteric vein. Having finished these two anastomoses the two Dacron pieces were connected to each other by a running 4/0 Prolene† suture, taking into account the angle of 20–30° the two vessels are making when the bowel is placed in the normal position to avoid torsion of the prosthesis. The pressure in the mesenteric vein was measured by direct puncture before and after creation of the shunt. All operations were performed by, or under supervision of, qualified surgeons in the department.

Postoperatively patients received a protein-restricted diet and, if indicated, lactulose and/or neomycin. Encephalopathy was assessed by patient signs and symptoms, information from relatives, physical examination and electro-encephalography. Encephalopathy was graded as: grade 1, changes in day–night pattern, lack of concentration; grade 2, slurred speech or apathy; grade 3, confusion or coma.

Patency of the shunt was determined at autopsy when the patient died in the hospital or by the following imaging techniques: scintisplenoportography and ultrasonography, complemented by angiography if findings of the former two investigations were contradictory. Patients were investigated 2 weeks after the operation and 1, 3, 5 and 10 years later, or earlier as symptoms or signs indicated.

The shunt was considered patent if, at scintisplenoportography, the radio-isotope reached the lungs and heart within 5 s without visualization of collaterals (*Figure 2*) and if the portal vein or mesenteric vein increased in calibre at the end of deep inspiration as demonstrated by ultrasonography.

Values are expressed as means ± s.e.m. Statistical analyses were carried out using the Mann–Whitney *U* test and the χ^2 test. The Kaplan–Meier method was used to calculate cumulative survival and patency rates.

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* *Dacron is a registered trademark of DuPont de Nemours Inc.*

† *Prolene is a registered trademark of Ethicon Ltd*

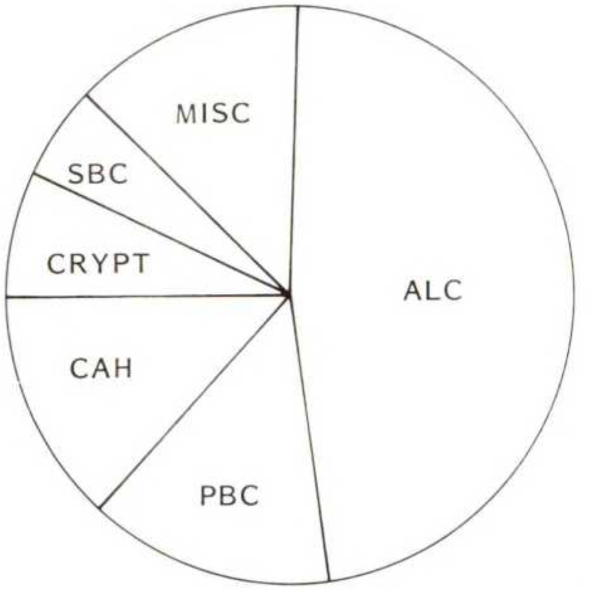

Figure 1 *Aetiology of cirrhosis in 64 patients. ALC, alcoholic liver disease; PBC, primary biliary cirrhosis; CAH, chronic active hepatitis; CRYPT, cryptogenic liver cirrhosis; SBC, secondary biliary cirrhosis; MISC, miscellaneous causes of cirrhosis*

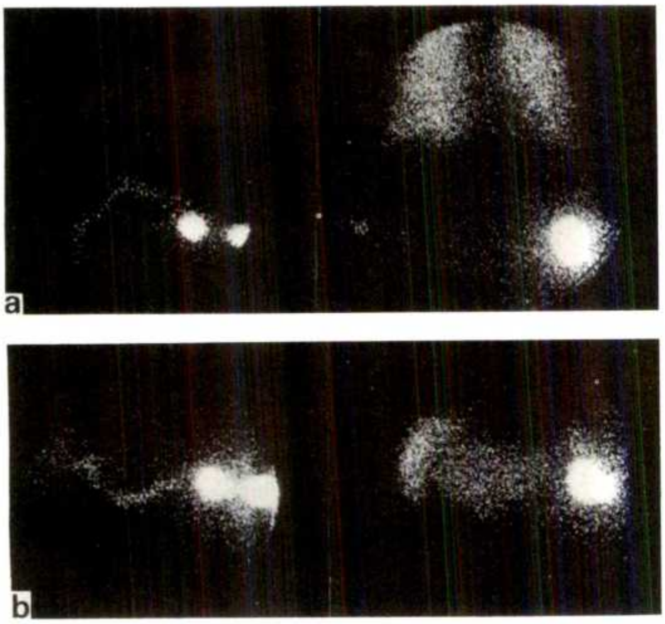

Figure 2a *Scintisplenoportography of a patent mesocaval shunt: the isotope, injected into the spleen, reaches the lungs within 5 s.* **b** *Scintosplenoportography of a thrombosed mesocaval shunt: visualization of the liver and collateral circulation*

Results

Operative findings

Pressure in the superior mesenteric vein decreased from 32·0 ± 1·2 mmHg to 15·2 ± 0·9 mmHg (52·4 ± 1·8 per cent) after creation of the mesocaval shunt. Duration of the operation was 209·1 ± 15·7 min in 32 patients who had emergency procedures and 222·0 ± 13·3 min in 32 patients who were operated as (semi)elective cases. Operative blood loss was 2600 ± 340 ml in acute operations and 1920 ± 270 ml in (semi)elective operations ($P < 0{\cdot}05$).

Early mortality

Within 30 days postoperatively, 17 patients (27 per cent) died from persistent or recurrent oesophageal bleeding (5), hepatic and renal failure (6), septic complications (5) and air embolism (1). Early mortality was 34 per cent for emergency operations and 19 per cent for delayed or elective procedures. *Figure 3* shows the operative mortality in relation to the Child classification and to the timing of surgery.

Encephalopathy

Of the 47 patients who survived beyond 30 days after the operation, 21 patients had no signs or symptoms of encephalopathy without additional medication other than a diet restricted to 60 g protein daily. Twenty-one other patients had to take lactulose and/or neomycin medication to prevent symptoms of encephalopathy whereas EEG recordings showed encephalopathy grade 1. Five patients were repeatedly admitted for encephalopathy grade 2 (four patients) or grade 3 (one patient). The latter patient died in hepatic coma.

Shunt patency

Patency of the shunt could not be evaluated in four patients, either because they died early after the operation and permission for autopsy was not given or because the patients refused follow-up studies. Shunt occlusion was demonstrated in six patients within 30 days after the operation. Five of these patients had persistent or recurrent bleeding from oesophageal or gastric varices. In 11 other patients the shunt, although patent at the time of discharge from the hospital, thrombosed after various intervals ranging from 4 to 99 months. Using the life-table method, cumulative occlusion rate was calculated. After 1 year 16 per cent of all shunts occluded; after 5 years the occlusion rate was 33 per cent and at 8 years follow-up 52 per cent of the shunts were occluded (*Figure 4*). Four of the eleven patients with a late occlusion rebled from varices.

Recurrent bleeding

Of the 47 patients who survived the operation longer than 30 days, 7 patients (15 per cent) experienced recurrent bleeding from oesophageal or gastric varices as demonstrated by oesophagogastroscopy. In three of these cases the shunt was patent, as demonstrated by angiography. Taking into account the patients who persisted in bleeding after the operation, 12 (19 per cent of all patients) rebled from their varices. Fall in portal pressure in the patients who had persistent or recurrent bleeding in spite of the mesocaval shunt procedure (50·0 ± 4·3 per cent) was not statistically different from that in patients in whom the shunt prevented further bleeding (52·9 ± 1·9 per cent).

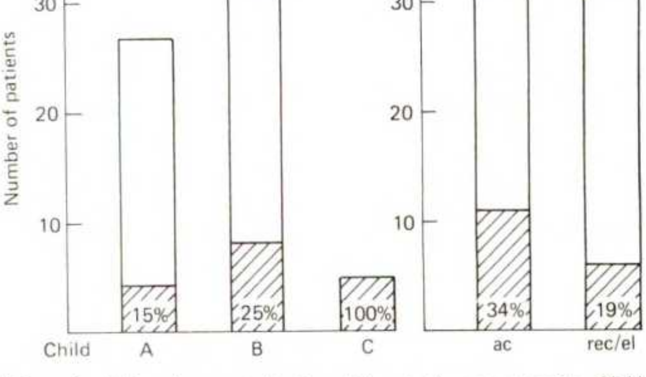

Figure 3 *Thirty-day mortality in relation to the pre-operative Child classification and the timing of the operation.* ▨, *number of patients that died within 30 days after the operation; ac, acutely operated patients; rec/el, patients that were operated after recovery from the bleeding episode or as an elective procedure*

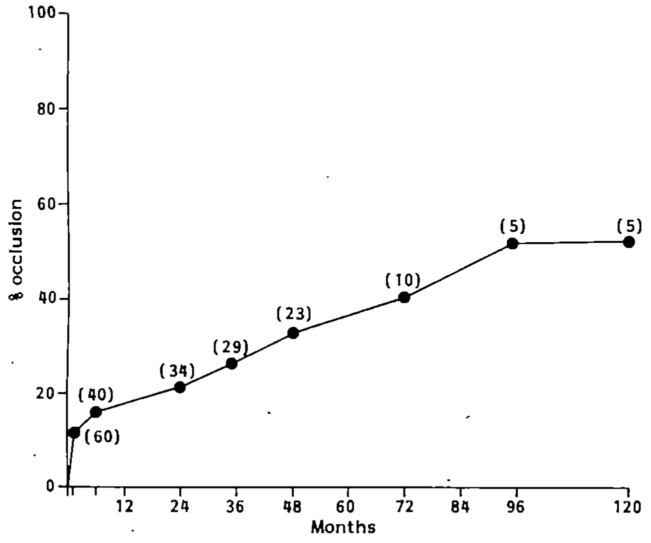

Figure 4 *Cumulative shunt occlusion rate. The numbers in parentheses refer to the number of patients at risk*

Long-term survival

The mean follow-up period was 49·2 ± 4·3 months. Patient survival is 61 per cent at 1 year and 39 per cent at 5 years (*Figure 5*). Major causes of death were hepatic failure (7) and stroke (3).

Discussion

Unlike American and French reports on portosystemic shunting, only half of our patient population suffered from alcoholic liver disease. This difference in aetiology of chronic liver disease obscures comparison with results as reported by others. However, the early mortality of 27 per cent in our study is similar to that reported by other authors with an equally high percentage of acutely operated patients[4–8].

In comparing emergency operations with (semi)elective procedures a significant difference in operative blood loss was noted, while the duration of the operation was equal in both patient categories. The greater blood loss in the emergency operations probably reflects the advanced stage of clotting abnormalities in these patients that contributes to an increased postoperative mortality. All patients with a poor pre-operative estimation of liver function (Child C) who needed an emergency operation died. In contrast, few patients with a good pre-operative liver function assessment (Child A) died of operative complications: of the nine patients in this category who were operated upon as an emergency two died, one from sepsis caused by aspiration pneumonia and the other from air embolism through a disconnected central venous catheter. Two other patients from the 12 Child A patients who were operated within 48 h of the bleeding episode died from hepatic and renal failure after relaparotomy for postoperative intra-abdominal bleeding. When electively operated, i.e. a few days to weeks after the initial bleeding, all patients with a good residual liver function survived the postoperative period.

The poor long-term survival of patients with serious chronic liver disease who experienced at least one major bleed is not surprising in the light of earlier reports.

Drapanas postulated in the early 1970s that hepatic encephalopathy occurred less frequently after the mesocaval shunt than after other types of portosystemic shunts that were commonly used at that time[1,9]. He argued that antegrade liver perfusion by portal blood still continues as the portal pressure diminishes by about 50 per cent after mesocaval shunting. We found a similar pressure drop in our patients. However, hepatopetal portal flow could be demonstrated in only a minority of the patients[10,11]. In the largest series of mesocaval shunting reported[2] the incidence of postoperative encephalopathy was 22 per cent. Comparison of encephalopathy rates in different series is impossible owing to the variety of definitions used. Postoperative manifest encephalopathy was present in only 9 per cent of our patients. This low incidence may be influenced by the death of encephalopathic patients within 30 days after the operation. Of the 64 patients, 17 were encephalopathic before the operation, and 12 (71 per cent) died shortly after the operation. This is in contrast with the 47 patients without previous signs of hepatic encephalopathy of whom 6 died in the postoperative period (13 per cent, $P < 0.05$ *versus* patients with pre-operative periods of encephalopathy).

Almost one out of every three shunts occluded, either early after the operation or at various time intervals thereafter. Only two other groups[12,13] reported similar high occlusion rates of the Dacron mesocaval interposition shunt of 24 per cent and 53 per cent, respectively. Other authors mentioned occlusion in 5–17 per cent of their shunts[2,5,6,8]. However, periodical evaluation of shunt patency was not carried out in these studies. Scintisplenoportography is a safe and reliable method to check patency of the shunt[14,15]. All cases of shunt occlusion, as demonstrated by scintisplenoportography, were confirmed at autopsy, laparotomy or angiography. Ultrasonography is useful in determining the patency of portosystemic shunts[16,17]. If a change in calibre of the portal or mesenteric vein during deep inspiration could be demonstrated ultrasonographically, the shunt was proven to be patent in all cases. On the other hand, lack of change in vessel size was not a definite indication of shunt occlusion, as some shunts subsequently were found to be patent at angiographic examinations. The high occlusion rate of mesocaval shunts may contribute to the alleged low incidence of postoperative encephalopathy. Possible causes contributing to shunt occlusion include 'kinking' of an over-long segment of prosthesis, external compression of the shunt by the duodenum and thrombogenicity of Dacron, especially in an area of low flow. Our modification in the technique as originally described by Drapanas[1] concerns the way the anastomoses between the prosthesis and the vessels are made. We used the same technique as in other vascular procedures[18]; each anastomosis is made with a separate piece of prosthesis, after which a prosthesis-to-prosthesis anastomosis is made. This facilitates correction for the angle between the vena cava and the superior mesenteric vein so torsion can be avoided.

To improve patency of an interposition shunt some authors advocate the use of other graft material such as polytetrafluoroethylene, claiming a shunt patency of 97 per cent at 18 months follow-up[19,20]. The use of autologous jugular vein has not found wide acceptance; in a controlled study the mesocaval shunt with jugular vein was no different, in terms of

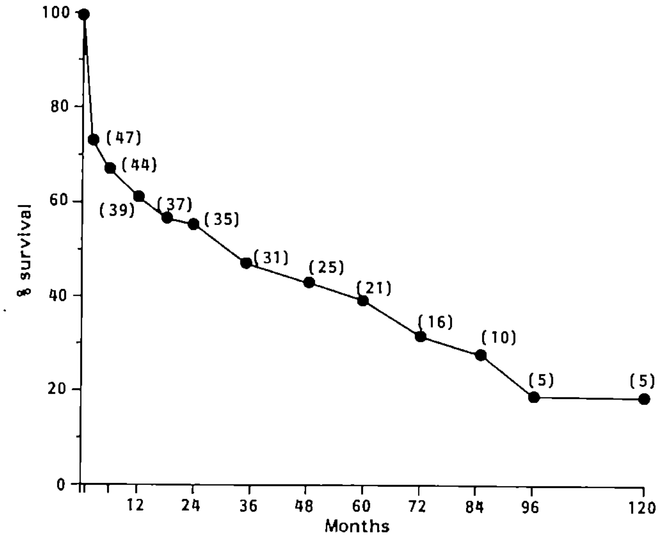

Figure 5 *Cumulative patient survival rate. The numbers in parentheses refer to the number of patients at risk*

operative mortality, hepatic encephalopathy and long-term mortality, from the side-to-side portacaval shunt[21]. Avoiding the interposition principle by direct anastomosis between the vena cava and the superior mesenteric vein might be another possibility[22]. Results from systematic evaluation of shunt patency are required before these alternatives can be recommended.

Of concern is the finding that three patients rebled from oesophageal varices in the presence of a patent shunt. This, together with the high incidence shunt occlusion, resulted in persistent or recurrent bleeding in 12 of the 64 patients (19 per cent). Thus, the first goal of shunt surgery, haemostasis and prevention of recurrent bleeding, was achieved in only 81 per cent of the patients treated with a Dacron mesocaval shunt. The high operative mortality, especially in emergency operations which are often needed for Child C patients, is prohibitive.

Endoscopic sclerotherapy has become the preferred method to arrest variceal bleeding[23,24]. If sclerotherapy fails to prevent further bleeding, shunt surgery can be indicated. In view of the high rate of thrombosis of the Dacron interposition mesocaval shunt we do not recommend this type of shunt. Only when anatomical abnormalities, like thrombosis of the portal or splenic vein or previous upper abdominal surgery, render the creation of a portacaval or distal splenorenal shunt difficult, should the use of a mesocaval shunt be considered.

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Evaluating surgical risk: the importance of technical factors in determining outcome

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A total of 113 patients having elective resection of the alimentary tract were studied prospectively to examine the relationship of pre-operative clinical and nutritional assessment to the development of major postoperative complications. In addition, the operating surgeon made a risk assessment on a linear analogue scale before and immediately after operation. Major complications developed in 28 patients (25 per cent). Age, weight loss and relative weight did not select high risk patients, but patients with a serum albumin of 29 g/l developed significantly more complications than those with higher levels (60 versus *22 per cent,* $P<0{\cdot}05$*). Clinical assessment also selected some high risk patients but patients selected by the surgeon's pre-operative assessment did not develop significantly more complications than those not selected (38* versus 21 *per cent). However, the surgeon's postoperative assessment did select patients at significantly increased risk, especially when compared with his pre-operative assessment. Of 38 patients who were selected pre-operatively as high risk or who increased their risk ranking postoperatively, 20 (53 per cent) developed complications, as opposed to only 6 of 65 patients (9 per cent) who were low risk or decreased their risk ranking* ($P<0{\cdot}001$)*. The surgeons changed their ranking postoperatively in 44 patients and in 36* (82 *per cent) the reason given was the technical ease or difficulty of the procedure. Using receiver-operating characteristic curves, immediate postoperative assessment was superior to any pre-operative method of selecting high risk patients. Of 15 patients with normal serum albumin levels whose risk ranking increased postoperatively 6 (40 per cent) developed complications while none of the 7 patients with low serum albumin (high risk) who decreased their risk ranking developed complications. It is concluded that operative performance is the main factor in the development of postoperative complications and should be assessed in future studies of outcome.*

Keywords: Risk assessment, postoperative outcome

In the last decade, there have been many investigations of the relationship between pre-operative nutritional state and postoperative outcome in patients undergoing surgical procedures[1–6]. These studies have suggested that abnormal anthropometric and biochemical measurements in association with protein–calorie malnutrition can identify patients at increased risk of developing postoperative complications. This had led to the suggestion that pre-operative nutritional support will reduce postoperative morbidity and mortality[7–9]. However, many surgeons remain sceptical of the place of prognostic formulae in clinical practice, and the use of nutritional support to reduce the incidence of postoperative complications has not gained wide acceptance. Surgeons recognize that many of the complications after surgery are operator dependent. Slipped ligatures and inadequate haemostasis, poor technique in anastomosis, obesity and variations in anatomy all may increase the probability of developing postoperative complications. Many of these difficulties have been recognized[10] but have not been evaluated in studies of nutritional status and outcome. The present study was set up to determine whether or not the technical aspects of surgery which contribute to a poor outcome can be quantified. The relationship of a surgeon's assessment of risk to an established prognostic measurement, serum albumin, has also been assessed.

Patients and methods

Patients

From September 1985 to May 1986, 113 consecutive patients scheduled for elective alimentary resection were studied prospectively. There were 53 women and 60 men with ages ranging from 28 to 93 years (median 64). Of the 79 patients with malignant disease, the oesophagus was the primary site in 6, the stomach or duodenum in 18, the small bowel in 2, the pancreaticobiliary system in 11, the colon in 40, the peritoneum in 1 and in another patient the primary site was unknown. Of the 34 patients with benign disease, 10 had pancreatitis, 8 had peptic ulcer disease, and the remainder included patients with malabsorption, bile reflux, diverticular disease, ulcerative colitis, arteriovenous malformations, recurrent sigmoid volvulus, biliary trauma, and benign neoplasms.

Operative procedures

All patients were given prophylactic antibiotics appropriate to the operation being carried out. Although a major gastrointestinal resection was scheduled in all patients, 7 had a laparotomy alone and another 8 had a change of operation. Of these patients, 4 had gastrointestinal bypass, 3 changed from abdominoperineal resection to anterior

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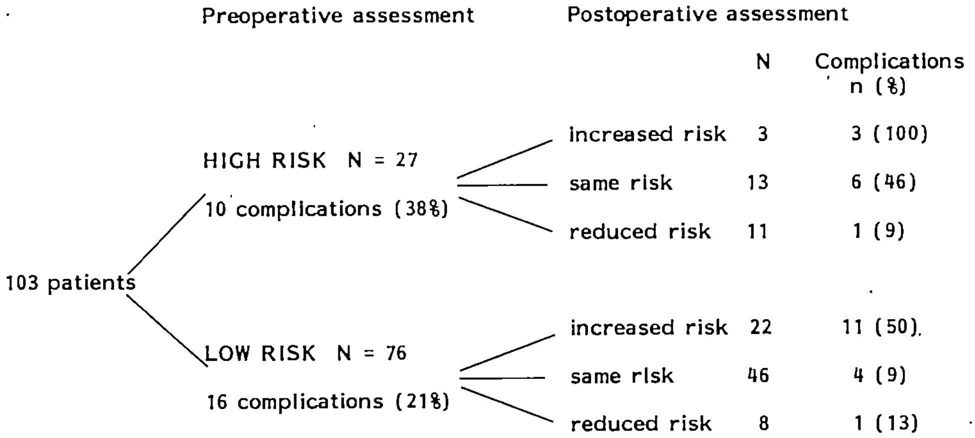

Figure 1 *Distribution of 103 patients with respect to the development of complications (percentages in brackets) and the pre- and postoperative assessment of the operating surgeons*

Table 1 *Operative procedures in 113 patients*

Procedure	Number of patients
Laparotomy only	7
Oesophagectomy	6
Gastrectomy	20
Gastro-enterostomy	6
Revisional gastric surgery	3
Cystogastrostomy	2
Pancreatic surgery	11
Hepaticojejunostomy	10
Small bowel resection	2
Right hemicolectomy	10
Left hemicolectomy	3
Sigmoid colectomy	6
Anterior resection	15
Abdominoperineal resection	7
Total colectomy	1
Closure of Hartmann's	4

resection or vice versa, and 1 patient had small bowel resection and colostomy revision instead of restoration of continuity following a previous Hartmann's operation. Five other patients had an additional procedure (1 cholecystectomy, 3 splenectomies, 1 partial hepatectomy). The operations undertaken are detailed in *Table 1*.

Clinical assessment

The day before surgery, each patient underwent a nutritional and clinical assessment. Weight and height were measured and patients were asked for a recalled well-weight. Relative weight (weight/height^2) and weight loss as a percentage of recalled well-weight were recorded. A sample of venous blood was withdrawn for serum albumin concentration (normal range 35–50 g/l). A clinical history was taken by one clinician (R.A.P.) with emphasis on medical risk factors, and a linear analogue scale was used to record the clinician's estimate of risk from these data. The scale was 100 mm long with lowest risk at the left end and highest risk at the right end. For each patient a mark was placed on the scale at a point appropriate to the clinical estimate of risk and patients were ranked according to the measurement (mm) from the left end of the scale.

Surgeon's assessment

On the morning of surgery, the surgeon recorded his assessment of risk of the patient developing major complications—on a linear analogue scale similar to that described above. Patients ranked above 50 mm on the scale were classified as high risk. After operation, on a second scale on the same form, he recorded his postoperative assessment of risk. For each assessment patients were ranked by the measurement from the low risk end to the surgeon's mark. Where there was a difference between pre- and postoperative assessments, the surgeon was asked to record a reason for the change.

Postoperative complications

Patients were followed up daily until death or discharge from hospital and major complications were recorded. Major complications were defined as follows: clinically apparent anastomotic leaks confirmed radiologically, intra-abdominal abscesses requiring drainage, myocardial infarction proven by ECG, cerebrovascular accidents with permanent neurological deficit, respiratory failure requiring mechanical ventilation, septicaemia proven on two separate blood cultures, pseudomembranous colitis proven on stool culture, wound dehiscence and any other postoperative event requiring reoperation and any cause of death. Wound, urinary and chest infections were not included as major complications.

Statistical analysis

For each assessment method, high and low risk groups were defined at nine cut-off points. The cut-off points chosen were at 10 per cent of the population assessed and then at 10 per cent intervals up to 90 per cent. The significance of differences in complication rate between high and low risk groups was determined by χ^2 test, or Fisher's Exact test when small numbers were being used[11]. At each cut-off point, sensitivity and specificity were calculated. The differences between assessments were demonstrated by constructing receiver-operating characteristic (ROC) curves, as described by Detsky *et al.*[12] and plotting true positive rate (sensitivity) against false positive rate (1 − specificity).

Results

Complications

Twenty-eight patients (25 per cent) developed major complications. Of the nine deaths, three were due to advanced malignancy, two to myocardial infarction and one each due to cerebrovascular disease, colonic infarction, pancreatitis and respiratory failure. Of the 19 patients who developed non-fatal major complications, 12 had leaking anastomoses (9 gut, 2 biliary, 1 pancreatic), 2 required reoperation for postoperative haemorrhage and there were 1 each with respiratory failure, septicaemia, cerebrovascular accident, pseudomembranous colitis and wound dehiscence.

Clinical assessment

When evaluating age, weight, relative weight or weight loss as risk factors, there were no significant differences in the complication rate between those patients identified as high risk and those as low risk at any cut-off point. However, patients below the 10 per cent cut-off for serum albumin (< 29 g/l) had significantly more complications than those with higher serum albumin levels (60 *versus* 22 per cent $\chi^2 = 6{\cdot}11$, $P < 0{\cdot}05$).

For the clinical assessment on the linear analogue scale, patients were graded from 6 to 74 mm (median 26 mm). Patients ranked above 55 mm (10 per cent cut-off) had significantly more complications than those lower on the scale (60 *versus* 22 per cent $\chi^2 = 5{\cdot}38$ $P < 0{\cdot}05$).

Surgeon's assessment

Operating surgeons failed to record an assessment in ten patients (two with complications). *Figure 1* shows the distribution of the remaining 103 patients according to the pre-operative and postoperative assessments. For pre-operative assessment, the measurements on the linear analogue scale varied from 2 to 96 mm from the low risk end (median 30). Although some patients classified as high risk developed complications (38 *versus* 21 per cent) the difference was not significant ($\chi^2 = 1\cdot91$). Postoperative assessment measurements ranged from 2 to 99 mm (median 29) and at almost all cut-off points significantly more patients selected as high risk developed major complications, compared with those selected as low risk. For example, using 50 mm to define high risk, the difference in complication rate between high and low risk groups is highly significant (56 *versus* 16 per cent $\chi^2 = 13\cdot72$, $P < 0\cdot001$). Of 25 patients who had their risk increased postoperatively, 14 (56 per cent) developed major complications while only 2 of 19 patients (10 per cent) who had their risk reduced postoperatively developed major complications ($P = 0\cdot002$ Fisher's Exact test). Of 38 patients who were ranked over 50 mm on the scale pre- and postoperatively or who increased their ranking postoperatively, 20 (53 per cent) developed major complications while of those 65 patients who were marked at less than 50 mm on the scale before and after operation or who dropped their ranking postoperatively 6 (9 per cent) developed complications ($\chi^2 = 23\cdot5$ $P < 0\cdot001$). Reasons given for increasing a patient's ranking were, the discovery of advanced malignancy (4), presence of inflammatory lesions (4) and unspecified technical difficulties (17). Reasons for decreasing a ranking were the performance of a less difficult procedure (4) and that the planned procedure was technically easier than expected (15).

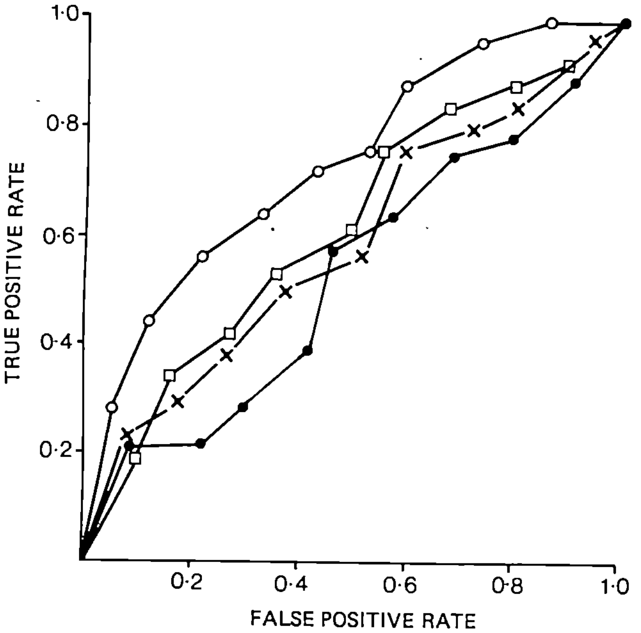

Figure 2 *Receiver operating characteristic curves comparing 4 methods of assessing 113 surgical patients.* ×, *serum albumin level;* ●, *medical assessment;* □, *pre-operative assessment;* ○, *postoperative assessment*

Sensitivity–specificity analysis

Figure 2 shows the ROC curves for serum albumin, medical assessment, and the surgeon's pre- and postoperative assessments. The essential features of ROC curves for evaluating nutritional assessment techniques have been previously described[12]. It is evident that the curve of the surgeon's postoperative assessment is superior to that of any other assessment curve, in that for any true positive rate there is a lower false positive rate.

Comparison of surgeon's assessment with serum albumin

Two patients assessed by the surgeons did not have a pre-operative serum albumin recorded. The remaining 101 patients are grouped by their surgeon's pre- and postoperative assessments and by serum albumin in *Table 2*. Of the 16 patients assessed by the surgeons as high risk pre- and postoperatively, there was a significant difference in complication rate between those with serum albumin < 35 g/l and those with albumin concentration > 35 g/l (80 *versus* 17 per cent, $P = 0\cdot02$ Fisher's Exact test). For the 20 patients changed to a higher risk ranking following operation, serum albumin concentration was not a significant determinant of complication rate (60 *versus* 40 per cent). None of 7 patients with serum albumin concentration < 35 g/l and ranked high risk pre-operatively but changed to a lower risk ranking postoperatively developed postoperative complications.

Discussion

The results confirm the finding that medical assessment or serum albumin estimation can identify patients at significantly increased risk of developing postoperative complications[6]. However, these methods of assessment are no better than the surgeon's pre-operative clinical judgement. Furthermore, immediately after operation the surgeon can identify significantly more high risk patients, with greater sensitivity and specificity, than any of the pre-operative assessment methods used in this study. Postoperative assessment not only selected a group of high risk patients who were not identified by serum albumin as high risk, but also recognized the reduced risk of some patients who were pre-operatively identified as high risk by their serum albumin. In this study, surgeons changed their risk assessment because of technical events that occurred at operation. These technical events were the most important identifiable cause of postoperative morbidity and mortality.

The study involved a heterogeneous population of high risk patients undergoing major gastrointestinal operations and this population is similar to that described in previous studies[1–6]. Medical risk assessment was done by one person not directly responsible for the patients' management while the linear analogue scale relies on a personal assessment of the operating surgeon's technical ability and skill. Although there is no standardization of the scale, this does not affect the main finding that it was the change in risk ranking postoperatively that improved the selection of high risk patients.

Table 2 *Influence of surgeon's assessment and serum albumin on the incidence of postoperative complications*

Surgeon's assessment				Serum albumin				
				< 35 g/l		> 35 g/l		
Pre-operative	Postoperative	No.	No. with complications (%)	No.	No. with complications (%)	No.	No. with complications (%)	P* 0·04
High	Same or higher	16	9 (56)	10	8 (80)	6	1 (17)	0·02
Low	Higher	20	9 (45)	5	3 (60)	15	6 (40)	n.s.
High	Lower	11	1 (9)	7	0	4	1 (25)	n.s.
Low	Same or lower	54	5 (9)	11	1 (9)	43	4 (9)	n.s.
All patients		101	24 (24)	33	12 (36)	68	12 (18)	

* Result of Fisher's Exact test. n.s., not significant

Nutritional surveys of surgical patients reporting a prevalence of protein calorie malnutrition of up to 50 per cent[13,14] have prompted the suggestion that pre-operative nutritional support may reduce surgical morbidity and mortality[7,8]. Clinical studies have identified a relationship between some nutritional measurements and postoperative complications in patients undergoing major gastrointestinal operations[1]. Among the many 'nutritional' indicators of risk advocated are weight loss[15,16], serum albumin and transferrin[5], hand dynamometry[3], various anthropometric measurements[1,3] and combinations of these in a 'prognostic nutritional index'[2] and its modifications[4,5]. Despite these observations, many clinicians remain sceptical of the value of nutritional support in surgical practice.

Other groups have suggested that pre-operative clinical assessment can identify high risk patients as well as any objective measurement. Baker and coworkers[17] showed that patients, classified as being 'malnourished' by two clinicians, had more episodes of sepsis, more antibiotics prescribed and a longer hospital stay than patients classified as not being malnourished. Although the patients they classified as malnourished had more abnormal nutritional measurements than those classified as normally nourished it is debatable if their 'subjective global assessment' was really assessing malnutrition alone[18]. Furthermore, it has been shown that ability to assess nutritional status depends on the training of the observer and that, even with training, a large proportion of malnourished patients are not recognized as such[19]. Nutritional assessments, therefore, seem to be lacking in definition and it is probable that many assessment techniques provide an index of illness rather than an index of malnutrition[20].

There are two main reasons why the surgeon, immediately after operation, should be able to identify correctly patients likely to develop postoperative complications. First, he may obtain new information regarding the pathology which may alter his assessment. In four patients in this study, the finding of cancer at a more advanced stage than expected was the reason for increased risk rating while in another four patients it was the finding of an inflammatory lesion such as an abscess which increased the surgeon's assessment of risk. Secondly and more importantly, the technical ease or difficulty of the procedure makes the surgeon change his assessment of risk. Four patients in the present study were submitted to a lesser operation (e.g. bypass instead of pancreatectomy) but, of the remainder who had their scheduled operation, it was technically more difficult in 17 and easier than expected in 15. Typical reasons for changed rating given by the surgeons were 'difficult anastomosis', 'resection more extensive' and 'operation proceeded better than expected'. The subsequent adjustment of risk level led to a dramatic improvement in the surgeon's predictive ability without any change of nutritional status.

To the clinical surgeon, operating is a technical skill acquired during training and developed with experience; most surgeons recognize that technical difficulties apparent at the time of operation can have an important influence on outcome. Wound dehiscence has almost been abolished by modern suture materials, attention to the ratio of wound length to suture length and adherence to correct principles of suture placement and tension[21]. Modern bowel anastomotic techniques and, arguably, the introduction of staplers have lessened the technical problems associated with anastomosis in difficult areas such as the lower rectum[22]. Obesity can be a greater technical challenge than cachexia in that the absence of fat allows clearer definition of critical structures and makes for easier surgery. To many surgeons the answer to improving postoperative outcome is not an improvement in pre-operative nutritional status, but improvement in operative skills. In these circumstances, malnutrition, with less fat to obscure vital structures, may almost be seen as an advantage. Furthermore, they realize that many of these 'malnourished' patients are malnourished because of the underlying pathology, often in the form of cancer, and early intervention will determine the extent of the disease and facilitate early recovery and discharge in patients whose life span may be very limited. In our opinion, therefore, further studies of the relationship between pre-operative nutritional assessment and postoperative outcome are pointless, unless account is taken of technical factors.

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Bilateral ankle skin temperature as a predictor of early vascular graft patency

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The efficacy of postoperative bilateral ankle skin temperature as a predictor of early graft patency was prospectively evaluated in 138 consecutive cases of femoropopliteal bypass surgery. The difference between ipsilateral and contralateral ankle temperature (hourly registrations) was significantly greater in the patients with patent graft on postoperative day 1 than in those with an occluded graft. In measurements 8 h postoperatively, highest sensitivity (84 per cent) and specificity (93 per cent) of the test were obtained when the difference was +0·4°C. The overall accuracy of prediction with this simple method was 89 per cent.

Keywords: Graft patency, bypass surgery, lower limb ischaemia, skin temperature

Most early failures of vascular reconstruction are attributable to technical errors[1,2], and timely detection of imminent graft failure can permit re-establishment of patency[3]. Hence it is important to recognize errors as early as possible, preferably before the patient has left the recovery room and with a non-invasive technique. Palpation of pulses in the extremities may be impeded by arterial disease, oedema, ulcerations or dressings. Measurement of the peripheral blood pressure and calculation of ankle/brachial index is a reliable method[4] but requires special training of recovery room staff.

The purpose of the present investigation was to evaluate the usefulness of bilateral ankle skin temperature as a predictor of early failure after reconstructive arterial surgery of the leg. The technique is simple and needs no special training.

Patients and methods

In a prospective study during 1981–1985, the skin temperature of both ankles was measured at the end of femoropopliteal bypass operations. Of the total 148 operations 10 were excluded, 6 because the contralateral leg had been amputated, and 4 because the early postoperative state of the graft could not be determined from the follow-up investigations.

Of the 138 evaluated operations, 87 were performed on men and 51 on women. The mean age at operation was 68 years (median 69, range 30–87 years). In 67 per cent of cases the Fontaine classification was III–IV. Some additional data are presented in *Table 1*. Ulceration was present in 25 per cent and gangrene in 14 per cent of the ipsilateral legs.

Autologous reversed saphenous vein graft was used in 75 (54 per cent) of the operations, polytetrafluoroethylene in 52 (38 per cent), composite graft in 6 (4 per cent) and umbilical vein graft in 5 (4 per cent). A total of 109 patients had a general anaesthetic and 29 epidural anaesthesia.

Skin temperature

Ankle skin temperature was measured hourly for 20 h postoperatively, using temperature sensors (YSI, model 409B, Kebo-lab, Stockholm) on the dorsum of both feet. The difference between temperature in the ipsilateral and the contralateral leg was calculated for each measuring occasion. Both feet were covered with a blanket, and the room temperature was approximately 23°C throughout the observation period.

Ankle blood pressure

Ankle and arm blood pressures were measured on the day before the operation, 1 and 3 days and 1 month postoperatively. Ankle/brachial pressure indices were calculated using the highest figure from measurements in the dorsal pedal or posterior tibial artery. An ordinary arm cuff and a Doppler flowmeter (Model 810, Parks Electronics) were used.

Patient groups

Patients were assigned to one of two groups according to assessment of graft patency on the first postoperative day. As angiography was not routinely performed on postoperative day 1, a variety of criteria had to be used.

The graft was judged to be patent (group 1) if at least one of the following was observed postoperatively (*Figure 1*): palpable peripheral pulses on days 1 and 3 and at 1 month and/or no symptoms and ankle/arm pressure index higher at 1 month than pre-operatively (a); angiographic evidence of graft patency (b); graft patent at later operation or at autopsy (c).

The criteria for classification as early graft occlusion (group 2) were: no peripheral pulses palpable and ankle/arm pressure index on day 1 ≤ pre-operative reading, or progression of symptoms with or without early amputation (a); angiography on day 1 showing graft occlusion (b); occlusion found at reoperation on day 1 (c).

This grouping was accepted as reference in calculations of diagnostic sensitivity and specificity[5] of the ankle skin measurements. The result was classified as positive (bypass occluded) if the temperature difference was less than a specified value, and negative (bypass patent) if the difference exceeded that value. Sensitivity denotes the incidence of positive test result in limbs with graft occlusion, and specificity is the incidence of negative result in limbs with patent graft.

Statistics

Values are expressed as the mean ± standard error of the mean. Parametric comparisons were made with Student's t test and non-parametric comparisons by the χ^2 test, utilizing Yates's correction when necessary.

Table 1 *Clinical characteristics of 138 cases undergoing femoropopliteal bypass*

Fontaine group	Pre-operative ankle/arm blood pressure index	Number of runoff vessels	Graft flow (ml/min)	Bypass below knee	Graft occlusion on day 1
II (n=46)	0·56 ± 0·02	2·5 ± 0·1	103 ± 12	(30·4)	(8·7)
III–IV (n=92)	0·35 ± 0·02	1·7 ± 0·1	98 ± 8	(60·8)	(15·2)
P values	< 0·001	< 0·001	> 0·05	< 0·01	> 0·05

The Table shows mean values ± s.e.m. Figures in parentheses are percentages

Results

Of the 138 grafts, 120 were classified as group 1 (patent) and 18 as group 2 (occluded) during the first 20 postoperative hours. Thus, occlusion rate was 13 per cent.

Skin temperature

In group 1 mean skin temperature in the ipsilateral legs increased with time after operation in almost linear fashion up to 9 h (approximately 31–35·5°C, $P<0\cdot001$), and thereafter remained relatively constant. In group 2 the temperature rise was slower. Contralateral legs also showed progressively higher temperature (30–33·5°C, $P<0\cdot05$).

The hourly differences in skin temperature between ipsilateral and contralateral leg in individual patients were calculated, and also means of these differences in both patient groups. In group 1 mean temperature difference increased to more than 2°C after 4 h and remained at a similar level in the later observation period. In group 2 the mean temperatures were higher in the contralateral than in the ipsilateral legs (temperature difference becoming negative). During the first 4 h, therefore, means of individual skin temperature differences showed progressive intergroup divergence, but thereafter the significant intergroup difference remained, by and large, constant (*Figure 2*).

Sensitivity and specificity

Group means are unsuitable for practical clinical use, which requires high accuracy in the prediction of graft status in individual patients. In our study the intergroup difference in temperature gradient was greatest 7–9 h postoperatively (*Figure 2*). We therefore used the 8-h registration for further statistical analysis. By calculating the sensitivity and specificity of various temperature differences for discriminating between patency and occlusion of graft 8 h postoperatively, we found +0·4°C to be the critical value, giving the highest sensitivity without loss of high specificity (*Figure 3*). At 8 h the specificity was 84 per cent and the sensitivity 93 per cent. This means that a temperature difference of $\leq +0\cdot4$°C between the two ankles 8 h after vascular reconstruction predicted around 90 per cent of the graft occlusions found at 1-day follow-up, whereas a difference of $> +0\cdot4$°C predicted a good result in around 80 per cent of the grafts that proved to be patent, giving 89 per cent overall accuracy.

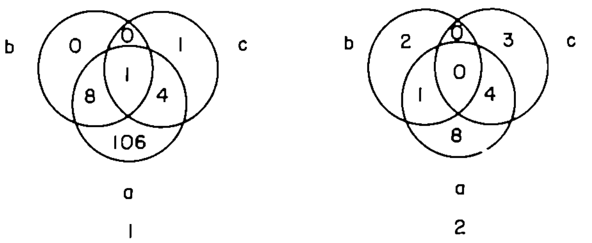

Figure 1 *Criteria for determining graft patency on postoperative day 1. a, peripheral pulses and ankle/brachial pressure index; b, angiographic findings; c, reoperation or autopsy findings; 1, patent grafts* (n = *120*)*; 2, occluded grafts* (n = *18*)

Discussion

Early failure of femoropopliteal grafts[6] occurs mainly when surgical procedure has been inappropriate for the extent of the disease or as a result of technical errors. Even when intraoperative angiography is routinely performed to detect technical failure a graft may become occluded in the postoperative period. Some type of postoperative monitoring is therefore necessary. In our experience, most early failures occur within the first 12–24 h and consequently assessment of graft patency is particularly important during that time. Moreover, if a vein graft is to be saved without extensive intimal damage, reoperation must be prompt[7]; hence, the monitoring procedure must permit continuous evaluation.

We found serial bilateral measurements of ankle skin temperature in the immediate postoperative period to be useful for predicting the early fate of femoropopliteal grafts. The result was correct in 89 per cent of the patients, and the procedure was easily performed by recovery room nurses.

Several methods are available for postoperative monitoring of femoropopliteal graft patency, but only measurement of ankle pressure has gained wide acceptance[4]. Although an accurate method special training in its use is required and, during the postoperative period, accuracy is hampered by incisions and dressings over the site for placement of the cuff. Oscillometry with a sling on the great toe may be clinically acceptable[8] but the results are more difficult to evaluate than are measurements of skin temperature.

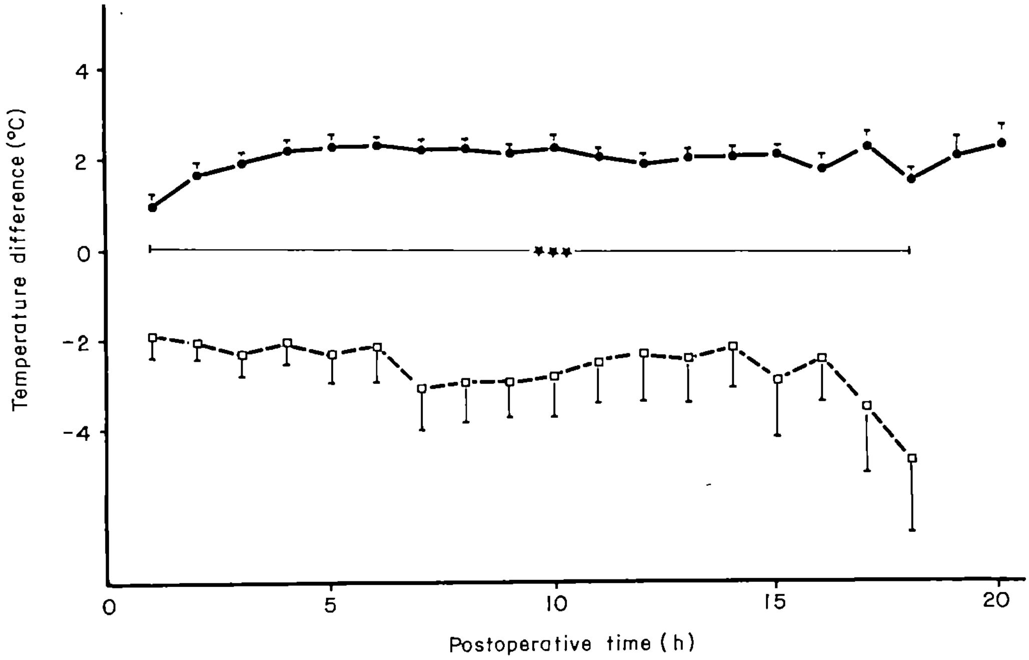

Figure 2 *Skin temperature differences between ipsilateral and contralateral ankle in the postoperative period.* ●, *group 1* (*patent*)*;* □, *group 2* (*occluded*)*. Means ± s.e.m.* ⊢ *** ⊣ *Indicates the time intervals during which the temperature differences are statistically highly significant* ($P<0\cdot001$)

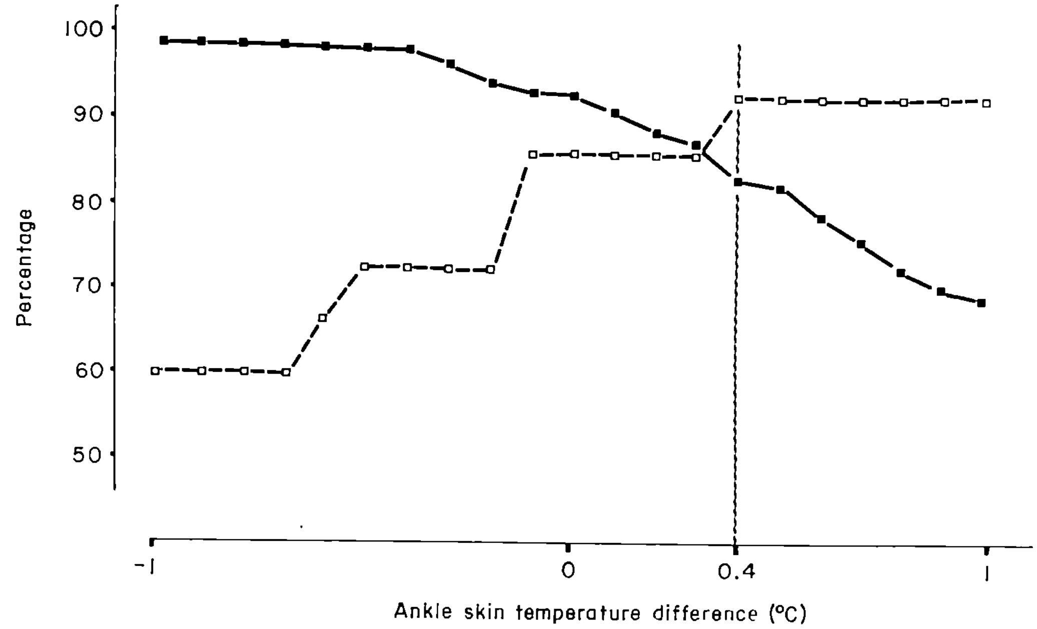

Figure 3 *Sensitivity* (□) *and specificity* (■) *of 8-h registration of ipsilateral–contralateral ankle temperature difference for predicting graft patency in groups 1 and 2*

Skin temperature has previously been used in quantification of arterial circulation, but is considered inaccurate because the temperature is affected by many factors other than arterial flow[9]. These factors include room temperature, variations in local temperature produced by blankets, dressings, sympathetic tone and loosening of applied temperature sensors. We circumvented most of these drawbacks by using the contralateral leg as control and basing the evaluation only on temperature difference between the legs. Recordings then followed a consistent pattern, with smooth progression of temperature change and, when steady state was reached, only small variations between measurements. By its nature, however, the method can be used only after unilateral operation in patients with two legs.

For correct judgement of our method's validity, accurate determination of graft status on day 1 is essential. Early postoperative angiography offers maximal precision in this respect but for ethical reasons it should be reserved for cases in which non-invasive monitoring has clearly suggested graft failure.

Clinical assessment of graft patency may be difficult on the first postoperative day. After a month the accuracy is acceptable for practical clinical purposes, though scientifically inadequate. The main problem is that graft occlusion may be masked by a substantial placebo effect of surgery. In our study, judgement of patency was based on clinical examination on three occasions. In all patients considered to have a patent graft there was clinical improvement, and all had either palpable pulses or ankle/brachial pressure index higher than the pre-operative reading. We believe that this assessment gave the highest accuracy achievable without angiography.

When graft occlusion is detected some weeks after vascular reconstruction, it is not always possible to decide the time at which the patency was lost. This uncertainty is illustrated by the four cases excluded from our series. The patients in group 2 almost certainly had graft occlusion on day 1.

The criterion of temperature difference should permit detection of as many failures as possible without including patent grafts in their number. The wider the chosen gradient the more complete will be detection of occlusion, but with proportionately heightened risk of wrongly classifying patent grafts. *Figure 3* shows that a criterion of +1°C would have identified 93 per cent of the occluded grafts, i.e. in 17 of the 18 affected legs the temperature was < +1°C higher than in the contralateral leg. Contrastingly, only 72 per cent of the patent grafts showed a temperature difference greater than +1°C and thus 28 per cent would have been falsely suspected to be occluded. At +1°C sensitivity was high but specificity low. If the criterion instead had been −1°C, only 60 per cent of the graft occlusions would have been detected, but almost all patent grafts correctly classified—low sensitivity but high specificity.

We found the best compromise to be +0·4°C, with sensitivity 93 per cent and specificity 84 per cent. When this criterion was used prediction of graft patency was wrong in only 15 of 138 cases, making the overall accuracy 89 per cent.

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Selective conservative and routine early operative treatment in acute limb ischaemia

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Arterial thrombo-embolectomy is often unsuccessful in those patients with acute limb ischaemia that have peripheral arteriosclerosis. During this study, conservative heparin treatment and, when needed, delayed surgery was employed in acute limb ischaemia when the ischaemia was less severe as judged by assessment of distal motor and sensory functions, regardless of the presumed aetiology of the acute ischaemia. The results are compared with those during a preceding period, when the routine treatment was emergency thrombo-embolectomy. The emergency operation rate was reduced to 49 per cent. There were overall fewer deaths with gangrene (8 per cent versus *18 per cent). In acute arterial thrombosis, more good results were obtained (76 per cent* versus *47 per cent), whereas results were unchanged in embolic cases despite the reduced emergency operation rate. This study suggests that the choice of initial treatment of patients with acute limb ischaemia may be based on the severity of the ischaemia, and that patients with less severe acute ischaemia benefit from initial conservative heparin treatment.*

Keywords: Arterial embolism, arterial thrombosis, embolectomy, heparin

Acute limb ischaemia is usually caused either by acute thrombosis in an artery narrowed by arteriosclerosis, or by arterial embolism which may affect normal as well as arteriosclerotic arteries[1].

A low amputation rate can be expected after embolectomy for acute embolic limb ischaemia, whereas the mortality rate is high[2]. Acute arterial thrombosis is reported to be associated with low mortality and low amputation rates when recognized early and initially managed either conservatively with intravenous heparin[3], or surgically with emergency bypass procedures[4]. By contrast, emergency thrombectomy alone in thrombosis which is treated as an embolic event is associated with a high rate of early failure and subsequent death[5], which may partly be due to metabolic, renal and cardiac disturbances by factors released from the ischaemic limb[1,2]. Revascularization of an acutely ischaemic extremity with advanced arteriosclerosis often requires endarterectomy or bypass procedures[1,4,5], even when the acute ischaemic event is presumed to be of embolic origin. These procedures require extensive experience of arterial surgery, but patients with acute limb ischaemia are initially often managed by a general surgeon with limited experience of vascular surgery.

It has been repeatedly stated that treatment of acute limb ischaemia should depend on early differentiation between arterial embolism and arterial thrombosis due to peripheral arteriosclerosis. Unfortunately, this differentiation is at times difficult[1,3,5–7], and the indications for initial non-operative treatment are still not clear. Peripheral arteriosclerotic lesions are thus commonly found in patients with embolic limb ischaemia[8]. In our opinion, the unsuccessful outcome of emergency thrombo-embolectomy is often due to peripheral arteriosclerotic disease, irrespective of the presumed aetiology of the acute ischaemia. Pre-existing collateral blood flow may limit the severity of the acute ischaemic event in patients with peripheral arteriosclerosis[9]. Instead of routine emergency thrombo-embolectomy in acute limb ischaemia, we have recently employed a selective conservative approach based on a simple clinical assessment of the severity of the limb ischaemia. The results are presented in this paper.

Patients and methods

The study group comprises 87 consecutive patients with 90 episodes of acute limb ischaemia during the years 1983–85. Two hundred and one consecutive patients, who during the period 1975–81 experienced 219 occlusive events, served as a reference group for comparison. Occlusive events after previous arterial reconstruction were not included. All patients were reviewed for their medical history, the duration of symptoms on admission, associated diseases, aetiology of the acute ischaemia, source and location of thrombi and emboli, and the type of treatment received.

During the years 1975–81, our routine treatment of patients with acute limb ischaemia due to arterial embolism or thrombosis was emergency thrombo-embolectomy by the duty surgeon and perioperative anticoagulant therapy, unless the ischaemia was very distal or the diagnosis was unclear. During this study (1983–85) duty surgeons were advised to avoid emergency surgery in cases with less severe acute ischaemia, regardless of presumed aetiology of the acute ischaemia. Severity of the acute ischaemia was assessed by evaluation of distal sensory and motor functions[9] and the state of the ischaemic muscle[3]. Initial conservative treatment was employed if the patient

Table 1 *Patient characteristics during the two studied time periods*

Characteristics	1975–81	1983–85
Average age (years ±s.d.)	77±8	78±9
Aetiology of acute ischaemia		
Definite embolism	(50)	(52)
Definite thrombosis	(23)	(22)
Uncertain	(27)	(26)
Recent (<2 weeks) myocardial infarction	(8)	(10)
Atrial fibrillation on admission	(53)	(59)
Upper extremity ischaemia	(16)	(17)
Previous history of intermittent claudication	(15)	(20)
Median duration of symptoms on admission (h)	12	12
Average annual incidence of acute limb ischaemia (*n*)	31	30

Numbers in parentheses are percentages. For each characteristic, there was found to be no significant difference in the results obtained in the two studied time periods

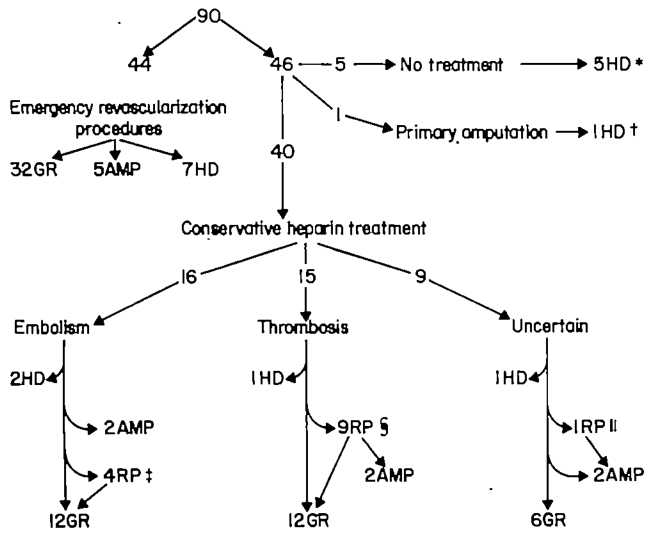

Figure 1 *Treatment and outcome of 90 events of acute limb ischaemia during the years of the study (1983–85). Presumed aetiology is noted in patients initially treated conservatively with heparin. GR, good results; AMP, amputations within 30 days; HD, death within 30 days; RP, revascularization procedure;* *, *three patients had multiple emboli involving the brain, one patient had gangrene with sepsis, and one patient had advanced cancer (all these patients had emboli and were moribund on admission);* †, *embolic ischaemia, gangrene on admission;* ‡, *two delayed embolectomies (30 h and 28 days after admission respectively) and two femoropopliteal reconstructions (2 and 16 months after admission);* §, *three thrombectomies with or without streptokinase infusion, three femorodistal reconstructions, two iliofemoral bypasses and one thrombendarterectomy with patch graft;* ‖, *femoropopliteal bypass*

adequately could perform toe (or finger) movements, had some perception of touch preserved distally in the affected extremity, and the ischaemic muscle was not tender. These patients were carefully observed and were given intravenous heparin (15 000–30 000 units/day for 4–7 days) followed by peroral warfarin therapy. The conservatively treated patients routinely underwent elective arteriography. Emergency arteriography, followed by semi-emergency or elective revascularization procedures when possible, was performed on limbs that failed to improve or deteriorated during conservative treatment. Patients presenting with severely compromised sensory and motor functions indicating imminent tissue necrosis[9] were given anticoagulant therapy and underwent emergency thrombo-embolectomy, unless the limb was clearly non-viable or the patient was moribund on admission.

A definite diagnosis of embolic occlusion was made when there was sudden onset of symptoms and a source of emboli in a patient without a definite previous history of intermittent claudication in the affected limb. A definite diagnosis of acute arterial thrombosis was made when there was rapid or sudden onset of symptoms of less than 7 days duration in the absence of a demonstrable cardiovascular source of emboli. These patients usually had signs or described previous symptoms of peripheral arterial disease in the legs. Aetiology in the remaining cases was considered to be uncertain. Hospital mortality was calculated within 30 days, amputation rate was calculated within 30 days on the 30-day survivors only, and a good result was defined as survival for more than 30 days without amputation. One-year survival was calculated by the life table method. The critical ratio of difference in proportions (with continuity correction) using one-tailed normal tables was used for statistical analysis.

Results

Patient characteristics in the study group (1983–85) and the reference group (1975–81) were similar (*Table 1*).

Treatment and findings during the study period

Emergency surgery was employed in 49 per cent of patients (*Figure 1*). Median duration of symptoms on admission was 24 h in those initially managed conservatively (*Figure 2*) and 6 h ($P<0{\cdot}01$) in those that underwent emergency thrombo-embolectomy. Conservative heparin treatment was used in 34 per cent of embolic events compared with 71 per cent of patients with thrombosis, demonstrating that the acute ischaemia more often was less severe in arterial thrombosis. Acute arterial thrombosis was common among patients seeking medical attention late (*Figure 2*).

Outcome of treatment during the study and the preceding period

Emergency thrombo-embolectomy was performed in 86 per cent of all cases during the reference period ($P<0{\cdot}01$ compared with the study period). There were significantly fewer episodes of gangrene with associated death in the study group (*Figure 3*). During the study period, good results were achieved in 75 per cent and 73 per cent of patients managed conservatively with heparin and those who underwent emergency thrombo-embolectomy respectively (*Figure 1*). Improved results (69 per cent *versus* 56 per cent, $P<0{\cdot}05$) were observed in iliofemoral occlusions ($n=58$ and $n=149$ respectively) during the study period compared with the earlier period, whereas the results in upper extremity occlusions ($n=15$ and $n=36$ respectively) were unchanged (80 per cent and 72 per cent good results).

During the study period, four patients (5 per cent) had limbs amputated between 31 days and 1 year after the acute event, compared with 11 patients (8 per cent, n.s.) during the reference period. One-year survival in patients that survived the first month was 81 per cent and 62 per cent respectively during the two time periods.

In definite arterial embolism, the overall results were similar during the two periods (*Table 2*). In the study group, 25 patients underwent emergency embolectomy, 1 underwent amputation as primary treatment, 5 received no specific treatment since they were moribund on admission and 16 were initially treated conservatively with heparin. Two of the latter patients died early, two had amputation (one of whom had a stroke contra-indicating early surgery) and four were later operated upon (*Figure 1*). Anticoagulant medication was continued permanently as the sole treatment in the remaining eight patients. In definite cases of acute arterial thrombosis, there were significantly fewer patients with gangrene and deaths

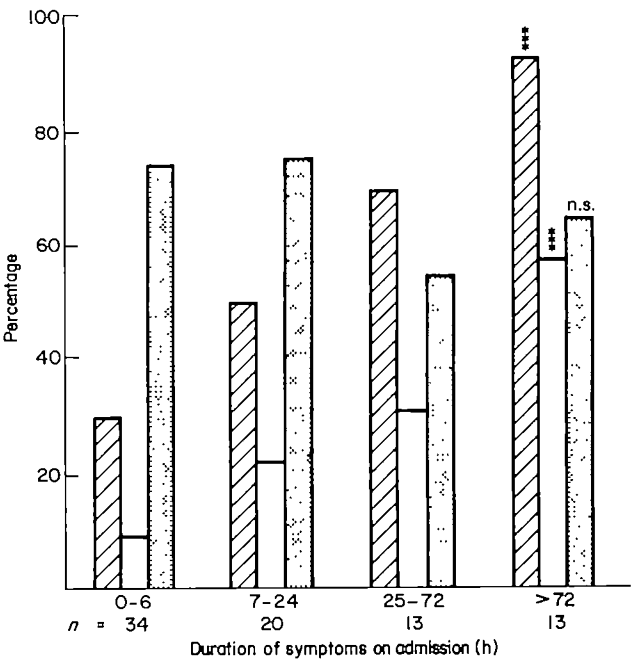

Figure 2 *Frequency of initial conservative treatment and acute arterial thrombosis as a function of the duration of symptoms on admission of patients with acute limb ischaemia during the study period. Success rates in these time intervals are also depicted.* ▨, *conservative treatment;* ☐ *acute arterial thrombosis;* ⬚, *good results; n.s., no significant difference, and* *** P<*0·01 (compared with cases admitted during the interval 0–6 h*)

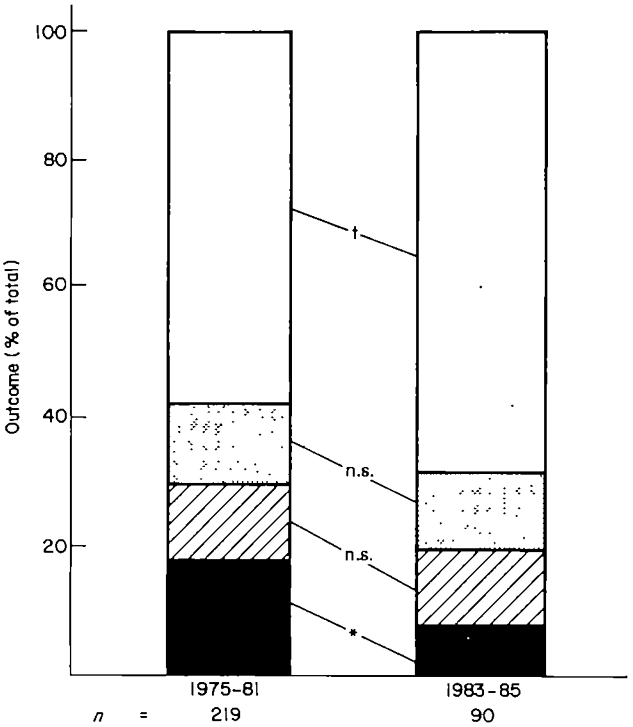

Figure 3 *Overall outcome of treatment during the reference period used for comparison (1975–81) and the study period (1983–85).* *, $P<0{\cdot}02$; †, $P<0{\cdot}03$: ■, *death with gangrene;* ▨, *death without gangrene;* ░, *amputed survivors within 1 month; and* □, *good results. Regardless of whether or not the patient survived for 1 month, 31 per cent of patients in the reference period and 20 per cent in the study period developed gangrene within 1 month* ($P<0{\cdot}03$)

Table 2 *Treatment and outcome in definite cases of arterial embolism*

	Study period ($n=47$)	1975–81 ($n=109$)	Difference
Emergency operation rate (%)	53	90	$P<0{\cdot}01$
Age (years ±s.d.)	(79±7)	(79±8)	n.s.
Outcome			
Good result (%)	68	63	n.s.
Hospital death (%)	26	29	n.s.
Amputation (%)	9	10	n.s.
Gangrene within 1 month* (%)	19	20	n.s.

Numbers in parentheses are the mean age of patients ± s.d. * regardless of whether or not the patient survived for 1 month

during the study period (*Table 3*). One patient of those initially treated conservatively in the study group died from a stroke during the first month and five patients improved early and received permanent anticoagulant therapy. The remaining nine patients failed to improve, and were operated upon (median duration from admission to elective bypass procedure = 7 days), with good results in seven patients (*Figure 1*).

Discussion

Tissues most sensitive to ischaemia in the extremities are the peripheral nerves and muscles[9]. Loss of skin sensibility and paralysis indicate severe ischaemia and the onset of tissue necrosis[1,9]. In a retrospective analysis, the initial severity of the acute ischaemia was suggested to be an important criterion for selecting patients for early operation[7]. Patients with acute limb ischaemia that have peripheral arteriosclerosis are reported to seek medical attention later than those without arteriosclerosis[4,5], a finding also noted in the present study (*Figure 2*). Pre-existing collateral blood flow limiting the severity of the acute ischaemia presumably explains this finding[9]; patients with arterial thrombosis in this study significantly more often had less severe acute ischaemia on admission than did patients with emboli. Emergency thrombo-embolectomy was avoided in cases with less severe acute ischaemia as judged by simple clinical parameters in this study, and this change in management was associated with fewer patients with early gangrene with associated death. Analysis of the two studied groups of patients suggested that patient selection or changes in the severity of the disease are very unlikely to explain the observed differences in outcome. Results were significantly improved in iliofemoral, and unchanged in upper extremity occlusions. Significant arteriosclerosis is common in the iliofemoral region, and may increase the hazards[10] of using the Fogarty catheter. In patients with arterial thrombosis the results were much improved and fatalities after failure of the operation were not observed during the study period but were common during the preceding period.

Emergency embolectomy is usually recommended in embolic limb ischaemia[2,3,5,6,9,11]. An overall limb salvage rate of 91 per cent of the survivors was observed in embolic occlusions during this study, in spite of the reduced rate of emergency embolectomies. Blaisdell and associates reported a low mortality rate using high-dose heparin treatment instead of embolectomy in an attempt to avoid possible negative effects of acute revascularization[12]. It seems that in patients with less severe embolic ischaemia even the moderate doses that we have used are effective—the mortality rate was low and only 25 per cent later needed vascular surgery.

After the use of the Fogarty catheter, thrombin activity appears on the endothelial surface[13]. If the postoperative blood flow is poor owing to arteriosclerotic stenosis, there is an increased risk of secondary thrombosis affecting the collaterals, thereby increasing the ischaemia[1]. Emergency bypass procedures may improve the results, in patients with acute limb ischaemia that have peripheral arteriosclerosis[4,7], but require extensive experience of arterial surgery. Although the value of heparin therapy before and after arterial thrombo-embolectomy in our opinion is unproven[14], our results suggest that collateral blood flow may be preserved by conservative heparin therapy until an adequate revascularization procedure can be performed, and heparin may even increase collateral blood flow by inducing angiogenesis[15].

Early distinction between embolism and thrombosis is frequently difficult[1,9,12], and was impossible even retrospectively in 26 per cent of the cases in this study. By contrast, distal motor and sensory functions and the state of the ischaemic muscle are usually easy to evaluate on admission. We suggest that the choice of initial treatment for patients with acute limb ischaemia can be based on an evaluation of these findings. Applying these principles, revascularization procedures, if necessary, can often be performed electively by a surgeon experienced in arterial surgery. Moreover, this management allows time to monitor the often critically disturbed cardiac function[12] of these elderly patients. The results of this study suggest that the present selective management improves results

Table 3 *Treatment and outcome in definite cases of acute arterial thrombosis*

	Study period ($n=21$)	1975–81 ($n=48$)	Difference
Emergency operation rate (%)	29	81	$P<0{\cdot}01$
Age (years ±s.d.)	(75±11)	(75±14)	n.s.
Outcome			
Good results (%)	76	47	$P<0{\cdot}03$
Hospital death (%)	5	35	$P<0{\cdot}02$
Amputation (%)	20	28	n.s.
Gangrene within 1 month* (%)	20	53	$P<0{\cdot}02$

Numbers in parentheses are the mean age of patients ± s.d. Also see *Table 2* in patients with acute limb ischaemia, mainly owing to improved results in patients that have arterial thrombosis.

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Announcement

Reviews

The Editorial Board of *The British Journal of Surgery* continues to invite review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium of £100. Potential authors seeking advice on the suitability of review topics are advised to contact: Professor D. C. Carter, University Department of Surgery, Royal Infirmary, Glasgow G31 2ER, UK.

Leading articles

The Editors invite submissions of signed leading articles to *The British Journal of Surgery*. These articles should be 600–1000 words in length, should address controversial topics of current interest and should be supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium of £100 is payable on publication. Potential authors seeking advice on the suitability of topics are advised to contact: Professor D. C. Carter, University Department of Surgery, Royal Infirmary, Glasgow G31 2ER, UK.

Surgical workshops

The Editors invite the submission of articles describing technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they can be accompanied by no more than two figures but should not carry supporting references. Articles submitted to the Surgical Workshop series may be subjected to external review and assessment by the Editorial Board before acceptance.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is likely to be high. Authors are advised to restrict such reports to a maximum of 500 words, to use no more than five references and to submit no more than one illustration.

Br. J. Surg. 1987, Vol. 74, September, 802–804

Reduced response of cerebral blood flow to hypercapnia: restoration by extracranial–intracranial bypass

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Cerebral blood flow, estimated by the xenon clearance technique, has been used to study eight patients before and after extracranial–intracranial (EC–IC) bypass surgery. Response of cerebral blood flow to hypercapnia was also measured to estimate cerebral reactivity, an indicator of cerebral vasodilator reserve capacity. Measurements in all patients were repeated 3 months after surgery. Resting cerebral blood flow was not increased by the operation but cerebral reactivity in the ipsilateral hemisphere was significantly increased in all patients (P = 0·002). Reactivity also increased in the contralateral hemisphere in six of the eight patients (P = 0·065). The response of cerebral blood flow to hypercapnia may prove useful in the selection of symptomatic patients with carotid occlusions or inaccessible stenoses for revascularization by EC–IC bypass.

Keywords: Cerebral blood flow, extracranial–intracranial bypass

Since the technique of superficial temporal artery to middle cerebral artery bypass (EC–IC) was first described by Donaghy and Yasargil[1], many of these operations have been performed with low morbidity and mortality[2,3]. Despite the technical success of the procedure and the high patency rates that have been achieved[4,5], the indications for the operation are still unclear[6,7], and a recent controlled surgical trial failed to show any decrease in stroke or death rates after operation when compared with those patients treated conservatively[8].

Up to the present time the clinical indication for surgery has been transient ischaemic attacks affecting a cerebral hemisphere supplied by an occluded internal carotid or middle cerebral artery (MCA), or an inaccessible stenosis of these vessels[9]. Most transient ischaemic attacks associated with a carotid stenosis are the result of a platelet embolism rather than reduced cerebral perfusion[10]. It has also been suggested that transient ischaemia attacks occurring in patients with carotid occlusion may result from an embolism arising in the upper end of the occluded artery or from the proximal stump of the internal carotid with the embolism passing through collateral channels[11]. Since EC–IC bypass cannot be expected to prevent such occurrences, it is important to try to restrict its application to those patients who are having 'haemodynamic' transient ischaemic attacks and who may have a limited capacity for vasodilatation (reduced cerebrovascular reserve). Haemodynamic attacks are short-lived and relate to episodes of vasodilatation resulting in 'stealing' from the cerebral circulation. They may be precipitated by exercise, posture changes and alcohol intake.

A simple method for looking at cerebral reserve is to measure the change in blood flow in response to an increase in inspired carbon dioxide which produces vasodilatation and increased blood flow in the normal brain[12]. We have used this technique to assess patients referred for EC–IC bypass. Eight patients who had transient symptoms in the hemisphere on the same side as an internal carotid occlusion or MCA stenosis and cerebral reactivities below the accepted normal range[13] were treated by EC–IC bypass. Angiography was repeated 3 months after operation to confirm the patency of the bypass, and cerebral reactivity was remeasured.

Patients and methods

Eight patients (7 men and 1 women) aged between 49 and 72 years (mean 63 years) were studied. Four had unilateral carotid occlusions with no significant carotid stenosis on the opposite side, three had bilateral carotid occlusions and one a middle cerebral artery stenosis. All patients had multiple attacks referable to a single internal carotid territory; six also had hand or leg transient ischaemic attacks, five experienced episodes of amaurosis fugax and three had both symptoms. CT scanning revealed the presence of small mature infarcts in the ipsilateral hemisphere of two patients. One patient with a tight external carotid stenosis underwent external carotid endarterectomy before EC–IC bypass in order to improve superficial temporal artery flow.

Xenon CO_2 reactivity

Approximately 7 mCi xenon-133, dissolved in normal saline, was injected into an arm vein as a bolus and flushed through with normal saline. Clearance of the isotope was monitored by three 25 mm scintillation detectors positioned over each hemisphere and the hemispheric blood flow was calculated from the means of the 1 min initial slope analysis of the three clearance curves. End expiratory xenon was continuously monitored to allow for the effect of arterial recirculation[14].

End expiratory P_{CO_2} was measured throughout the study using a Datex CD-300 infra-red analyser. This was assumed to reflect arterial P_{CO_2} concentrations.

One hour after the initial injection the cerebral blood flow measurement was repeated with the patient inhaling a mixture of 5 per cent CO_2 and 95 per cent air. This delay allows sufficient time for excretion of the first dose of xenon.

The study was performed pre-operatively and repeated once, 3 months after surgery. Reactivity was expressed as the percentage change in cerebral blood flow in ml 100 g^{-1} min^{-1} per mmHg change in P_{CO_2}. The normal value is $>3·5$ per cent mmHg^{-1}. Results were analysed using the Mann–Whitney *U* test.

EC–IC bypass

Superficial temporal to middle cerebral artery bypass was performed through a burr hole centred 5 cm above the external auditory meatus. The posterior branch of the superficial temporary artery was anastomosed to a cortical branch of the middle cerebral artery with interrupted 10/0 nylon sutures. An operating microscope was used for the anastomosis. The anterior branch of the superficial temporal artery was ligated at the end of the procedure. All operations were performed by one author (K.G.B.).

Results

Patients

Six patients had no further transient ischaemic symptoms after operation. Transient symptoms continued in two patients but diminished in both duration and severity. One patient died of a cerebral infarct involving the operated hemisphere 18 months after EC–IC bypass. A post mortem was not obtained and aetiology of the stroke remains unknown. The remaining seven patients are alive and well between 9 and 24 months after surgery, all with patent bypasses demonstrated at 3 months.

Cerebral blood flow and reactivity measurements

Mean hemispheric cerebral blood flow of the operated hemisphere before the EC–IC bypass was 32·2 ml 100 g^{-1} min^{-1} (range 28·7–36·0) and in the unoperated hemisphere it was 33·4 ml 100 g^{-1} min^{-1} (27·0–36·7). Using the formula described by Bullock *et al.*[13], the age-corrected expected mean cerebral blood flow in this age group should have been 36·3 ml 100 g^{-1} min^{-1}. Mean hemispheric cerebral blood flow after operation fell to 30·1 ml 100 g^{-1} min^{-1} (range 27·3–33·6) in the ipsilateral hemisphere and 30·8 ml 100 g^{-1} min^{-1} (27·0–35·3) in the unoperated hemisphere. The decrease in cerebral blood flow was not statistically significant.

Initially, mean reactivity to hypercapnia of the eight patients was 0 per cent mmHg^{-1} (range $-2·5$ to 1·8) in the operated hemisphere, and this increased significantly to 2·5 per cent mmHg^{-1} (0·5 to 4·4) following bypass ($P = 0·002$). In the unoperated hemisphere the mean pre-operative reactivity of 1·3 per cent mmHg^{-1} (range $-0·9$ to 3·8) increased to 2·7 per cent mmHg^{-1} ($-1·0$ to 4·8) postoperatively ($P = 0·065$). Reactivity of the operated hemisphere increased in all patients and improved on the unoperated side in six of the eight patients (*Figure 1*).

Discussion

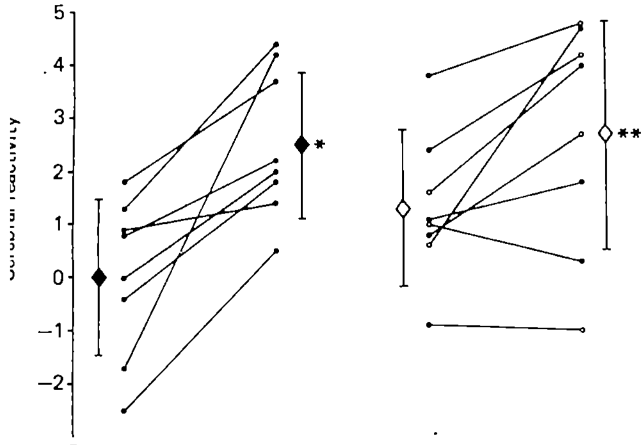
Gibbs *et al.* have shown that simultaneous measurement of cerebral blood flow and cerebral blood volume relates well to the localized oxygen extraction ratio of the brain, and they used this as an indication of cerebral metabolic demand[15]. Their sophisticated but expensive technique suggested that the ratio of cerebral blood volume to cerebral blood flow was increased in relation to the oxygen extraction or metabolic demands of the brain in some patients with carotid occlusion. They felt that ratio of volume to flow represented an index of cerebral reserve and suggested it might be valuable when selecting candidates for EC–IC bypass surgery.

We have assessed cerebral reserve by measuring the response of cerebral blood flow to hypercapnia and have confirmed a reduction in this response, which has been found by others in the symptomatic hemisphere of patients with carotid occlusions[13,16]. Our patients also had low resting cerebral blood flows but these were not improved by bypass. Indeed, resting cerebral blood flow decreased in our patients in both the unoperated and operated hemispheres. One explanation for this surprising finding may be that flow is lower during the second test because the patient is familiar with the process and less anxious.

The low reactivity to CO_2 in these symptomatic patients supports the hypothesis that transient ischaemic attacks in this group may be haemodynamic rather than embolic in origin. Haemodynamic attacks are unlikely to respond to medical management and, therefore, this group may benefit from surgery which provides another collateral pathway.

We have shown that the response to hypercapnia is significantly improved by EC–IC bypass. Pre-operatively cerebral reactivity in the operated hemisphere was below normal in all patients. Three months after operation it had reached the normal level in three patients, and had increased in the other five patients (*Figure 1*). These results, therefore, provide objective evidence that EC–IC bypass is having an effect on the cerebral circulation and that the efficacy of the operation may be assessed by a postoperative reactivity study. Improved reactivity in the contralateral hemisphere may result from a reversal of intracerebral steal[17].

Results from the EC–IC Bypass Study Group suggest that EC–IC bypass does not protect against fatal or non-fatal stroke in patients with occlusion of the internal carotid artery[8]. Furthermore, none of the other subgroups (middle cerebral stenosis, distal carotid stenosis, bilateral internal carotid occlusion or stenosis) showed any benefit. It appears that there are no clinical or angiographical criteria by which patients likely to benefit from the operation can be identified. However, there was no provision for cerebral blood flow or reactivity measurements in the protocol of this trial[18] and before the procedure becomes discredited it may be wise to consider whether such physiological measurements are able to identify a subgroup capable of benefiting from revascularization. Further evaluation of the prognostic value of the CO_2 reactivity test is necessary and this may be more easily achieved using a recently developed non-invasive transcranial Doppler method[19].



igure 1 *Effect of EC–IC bypass on cerebral reactivity in the ipsilateral emisphere (filled symbols) and the contralateral hemisphere of eight atients: Diamonds refer to means ± s.d., * P = 0·02, ** P = 0·065 (Mann–Vhitney U test)*

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Case report

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Pseudo-aneurysm of the profunda femoris artery following a stab wound

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Pseudo-aneurysm is an uncommon complication of stab injuries[1–3] and damage to the profunda femoris artery is rare[1–4] after a stab injury to the thigh.

Case report

A 21-year-old man was admitted with a 0·5 cm stab wound to the posterolateral aspect of the left thigh, sustained a few hours previously. The wound was sutured, tetanus toxoid and penicillin administered, and he was allowed home. Several hours later the wound started to swell and he was admitted under our care with a pulse of 84/min and a blood pressure of 110/60 mmHg. The patient's left thigh was grossly swollen and bruised, but there was no external haemorrhage. A loud systolic bruit was audible over most of the thigh. Despite a normal pulse pattern in the injured limb, the left foot was noted to be cold, and the patient complained of a pulsating pain in the affected thigh. A presumptive diagnosis of a pseudo-aneurysm was made.

The haemoglobin was 11·5 g/dl and white blood count 20·9 x 10/litre. The following day the haemoglobin was 9·0 g/dl and he was transfused 3 units of blood. Angiography revealed a large pseudo-aneurysm of one of the terminal branches of the left profunda femoris artery (*Figure 1*). Embolization of the lesion was considered to be the treatment of choice and accordingly selective catheterization of the profunda femoris artery was carried out under screening control. Three coiled springs were inserted, one proximal to the defect, one in the defect and one just distal to the defect (*Figure 1*). This procedure resulted in complete resolution of the pain and the bruit.

Five days later repeat angiography confirmed satisfactory resolution of the pseudo-aneurysm. The patient remains asymptomatic at 3 months.

Discussion

Traumatic pseudo-aneurysm is an uncommon complication of penetrating vascular injuries, occurring in 0·8–3·7 per cent in reported series[1,2]. Sampliner[3] describes seven cases of injury to the profunda femoris artery in a series of 124 cases of vascular injuries occurring in a civilian population. Since the profunda femoris artery is, anatomically, relatively inaccessible, surgical management—ligation or reconstruction—may be difficult. Accordingly, therapeutic embolization offers an attractive alternative in selected cases.

Sclafani[5] successfully employed this technique in four out of seven patients treated for penetrating gunshot injuries to the profunda femoris artery. The potential complication of muscle ischaemia is uncommon presumably because of the rich collateral blood supply, but embolization is contra-indicated in the presence of localized infection.

Embolization of a pseudo-aneurysm can be a satisfactory alternative to surgery in areas of difficult anatomical accessibility.

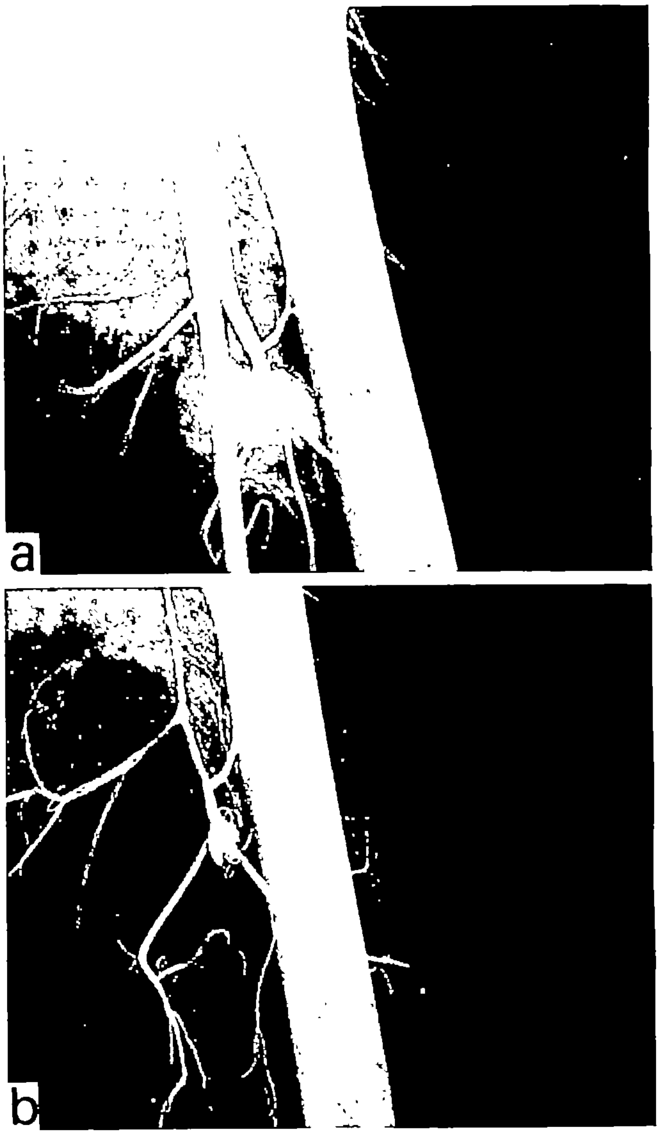

Figure 1 *The arteriograms show* (**a**) *a pseudo-aneurysm of the terminal branch of the left profunda femoris artery and* (**b**) *the response to the insertion of three coiled springs*

Acknowledgement

We would like to thank Mr G. MacBain for his permission to report this patient who was treated under his care.

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Pre-operative albendazole therapy for hydatid cyst

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Surgical management of hydatid cyst is associated with recurrence in 10 per cent of patients. The role of perioperative chemotherapy in prevention of recurrence has not been extensively explored. Sixteen patients with Echinoccus granulosus *were treated with albendazole 10 mg kg*$^{-1}$ *before operation; of fourteen patients who received albendazole for 1 month or more before operation only one (with doubtful therapeutic compliance) had viable protoscoleces, in contrast both of the two remaining patients who received only 1 and 3 weeks therapy had live disease at the time of operation. A 1 month pre-operative course of albendazole kills most if not all protoscoleces within hydatid cysts in man. This may allow pre-operative 'sterilization' of cysts and a reduction in the risk of recurrence.*

Keywords: Liver, hydatid cyst

One of the most significant problems in hydatid cyst surgery is recurrence which occurs in approximately 10 per cent of patients[1,2] and when recurrent disease occurs further surgery is associated with increasing operative morbidity and mortality[3]. The three most important causes of recurrent disease are small cysts missed at the first operation, re-infection and spillage. Improved pre- and perioperative imaging techniques may reduce the number of cysts which are missed and national or regional disease control schemes may reduce the risk of re-infection, but there has been little recent advance in the prevention of spillage/implantation. It is well established that spillage is dangerous; approximately 30 per cent of patients with peritoneal spillage can be expected to develop recurrent disease[4].

The use of scolicidal agents on operative packs to limit the consequences of spillage has become routine practice. However, significant systemic toxicity has been seen with formalin[5,6] and local toxicity in the form of adhesions has been recorded following the use of cetrimide[7]. Cyst–biliary fistulae are common in patients with large hepatic hydatid cysts[8] and injection of scolicidal agents into the cyst in order to sterilize its contents before opening the cyst is associated with a significant risk of developing sclerosing cholangitis, which has been seen following the use of formalin, ethanol, hypertonic saline and silver nitrate[9–11].

The purpose of this study was to determine the effect of pre-operative albendazole therapy on the viability of hydatid cysts in man.

Patients and methods

Sixteen patients with suspected *Echinococcus granulosus* were treated with albendazole 10 mg kg^{-1} day^{-1} orally. All patients had twice weekly liver function tests, white cell and platelet count and urinalysis. Female patients were warned of the potential teratogenic and embryotoxic properties of the drug.

The length of therapy used was variable. It was our policy to aim to treat for at least 1 month before planned surgery; six patients underwent surgery after apparent failure of chemotherapy. All patients in this study underwent surgery and at the time of operation cyst contents were aspirated after placement of packs soaked in 0·5 per cent silver nitrate by means of a syringe, needle and three way tap before the injection of any scolicidal agent. By altering the direction of the needle it was always possible to obtain an adequate sample. If bile stained fluid was aspirated (or if cyst–biliary fistula had been diagnosed previously by endoscopic retrograde cholangiopancreatography) no scolicidal agent was injected. The cyst was then emptied by a large diameter suction device which reliably removes daughter cysts and laminated layer without blockage[12]. Further operative management of the ectocyst cavity was conventional[8].

Viability assessment

Immediate microscopy of the aspirated cyst fluid was carried out to look for protoscoleces and their viability was assessed by flame cell activity, motility and ability to exclude 5 per cent aqueous eosin. Except for two of the first patients (when facilities were not available) gerbil intraperitoneal inoculation was also performed using 1 ml of the remaining fluid (approximately 5000 protoscoleces ml^{-1}) and also a preparation of daughter cysts or laminated and germinal layer. If the specimen was thought to be infected it was treated for 24 h in *in vitro* culture media containing antibiotics (gentamycin, streptomycin and penicillin) which do not affect parasite viability[13] and gerbils were treated with ampicillin for 24 h following inoculation.

Results

In all, 16 patients were studied (*Table 1*). The site of the cysts was hepatic in 12, bone in 2, peritoneal, retroperitoneal, anterior abdominal wall and cerebral in 1 each. The size of the cysts is shown in *Table 1*. Whilst it was intended to treat patients for at least a month before operation, two patients received 1 and 3 weeks therapy because delay was considered inadvisable in the first patient with a cerebral cyst and therapy was discontinued after 3 weeks owing to mild hepatotoxicity[14] in the other. One patient (no. 5) admitted taking her albendazole therapy erratically. All but one of the hydatid cysts were flaccid, in marked contrast to the tense cysts seen in untreated disease.

Macroscopic findings were not otherwise different from untreated hydatid cysts, all 12 hepatic cysts appeared to contain purulent or bile stained fluid and 10 had clearly identified biliary communications. Only one patient (no. 38) of the twelve patients where daughter cysts were found had tense daughter cysts.

Viability testing only identified three patients with live protoscoleses; all three were identified by microscopy and one was also positive by gerbil passage (three of four gerbils inoculated developed a total of eleven cysts). No patients have developed recurrent disease with a median follow-up of 15 months (range 2–34).

Discussion

The contribution of chemotherapy to the management of hydatid disease is growing. In 1977 Bekhti[15] described encouraging results in four patients treated with mebendazole, and considerable experience now exists with this compound[16]. Albendazole is another benzimidazole carbamate which achieves high serum and cyst fluid[17] concentrations of its principal metabolite albendazole sulphoxide. We have shown this metabolite to be an active scolicidal agent in *in vitro* cultures[13] in an animal model[18] and encouraging clinical and radiographic evidence of regression of cysts have been seen in man[19]. The possible contributions of perioperative chemotherapy in hydatid disease offer a prospect of reducing or perhaps completely preventing recurrent disease.

Table 1 *Details of the 16 patients studied*

Patient	Sex	Site of cyst	Diamter (cm)	Therapy (weeks)	Biliary communications	Viability Microscopy	Viability Gerbil	Follow-up (months)
4	F	Pelvic peritoneal DC	10	12		–	–	15
5	F	Hepatic DC	20	4	+	+	ND	34
6	F	Hepatic	20	4		–	ND	34
11	F	Hepatic DC	25	12	+	–	–	24
18	M	Hepatic DC	15	8	+	–	–	21
21	F	Hepatic	10	8	+	–	–	12
27	M	Anterior abdominal wall	5	8		–	–	29
29	F	Hepatic DC	25	12	+	–	–	21
30	M	Hepatic+bone DC (femur)	10	12	+	–	–	14
36	F	Bone (vertebral) Retroperitoneal DC	10	4		–	–	18
37	F	Hepatic DC	15	4	+	–	–	15
38	M	Hepatic DC	15	3*	+	+	–	11
43	M	Cerebral	8	1*		+	+	9
45	M	Hepatic DC	15	4	+	–	–	8
47	M	Hepatic DC	10	8	+	–	–	5
48	F	Hepatic DC	15	8		–	–	2

ND, not done; DC, daughter cysts; * short course of therapy due to hepatotoxicity (38), urgency of surgery (43)

The viability rate of symptomatic cysts in man is not clear but 6 of 12 patients operated on following mebendazole therapy were found to have definitely viable disease[20]. In this study only 1 of 14 patients who had at least a 1 month course of therapy was found to have live disease at operation and this patient admitted (before operation) having taken her medication erratically. It is of importance that both of the two patients who received less than a month's therapy had viable disease at operation. All viability tests should be interpreted with caution; a positive finding has more meaning than a negative one but the finding of live disease in these two patients who had an inadequate course strengthens our belief that an adequate pre-operative course of albendazole does significantly reduce viability of cysts.

It is also interesting that the only patient who produced cysts when protoscoleces were passaged into gerbils had been treated for only 1 week. This may mean that whilst protoscoleces appeared alive on microscopy in patient 38, they may have already been irreparably damaged by the 3 weeks albendazole therapy.

Whilst these data are most encouraging, pre-operative therapy may not be the optimum way of preventing recurrence. In the postoperative setting only a 'few' spilled protoscoleces need to be killed and problems with penetration of the drug into the cyst are avoided. We have previously shown that very short courses of albendazole following peritoneal spillage in gerbils significantly reduces the number of cysts which develop[21].

These concepts will require large long-term controlled clinical trials to establish that perioperative chemotherapy does prevent recurrence but this paper strongly suggests that a pre-operative course of albendazole $10\,\mathrm{mg}^{-1}\,\mathrm{kg}^{-1}\,\mathrm{day}^{-1}$ for 1 month significantly reduces viability of hydatid cysts in man.

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Resection in chronic pancreatitis

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In the absence of ductal ectasia there is no adequate alternative to pancreatectomy for severe chronic pancreatitis. A personal series of 30 such patients operated upon between 1977 and 1984 included 16 with distal pancreatectomy, 6 with proximal pancreatectomy and 12 with total pancreatectomy; 4 patients progressed from distal to total resection after an interval of 15–28 months. The mean age was 39 years with a male preponderance of 77 per cent. The main aetiological agents were chronic alcoholism (63 per cent) and previous acute pancreatitis (23 per cent). One patient died after total pancreatectomy, giving a 30-day mortality rate for all resections of 3 per cent. Postoperative complications necessitated reoperation in 10 per cent, and there have been 5 late deaths (17 per cent). Among 27 patients followed for a median of 4·5 years, pain relief has been good in 16, fair in 8 and poor in 3 (11 per cent). Proximal pancreatectomy has proved superior to distal pancreatectomy with regard to analgesia and the avoidance of diabetes. Although technically demanding, total pancreatectomy has improved symptoms substantially in 9 of 10 patients surviving for a minimum of 18 months.

Keywords: Chronic pancreatitis, pancreatectomy

The proper management of chronic pancreatitis provides one of the greatest challenges in abdominal surgery. Many patients with this disease are addicted not only to alcohol but also to the narcotic drugs taken to relieve their crippling pain; attendant psychosocial problems are only too common. The pancreas is closely related to several viscera and major blood vessels and becomes densely bound to these structures in the presence of chronic inflammation. This fact contributes to the high morbidity rates that accompany a direct surgical attack on the gland. Nevertheless unrelenting pain, pseudocyst formation and local compression syndromes often demand operative relief in this relatively young group of patients.

For those with pancreatic ductal ectasia, drainage of the main duct into a Roux loop of jejunum is probably the optimal procedure. Longitudinal pancreaticojejunostomy offers an excellent chance of analgesia lasting several years, even though the reason for its effect is not entirely clear[1,2]. It also avoids both mobilizing the pancreas from its bed of inflammatory scar tissue and the loss of function implicit in any type of resection. Unfortunately at least half the patients with chronic pancreatitis, including many of those with the most severe manifestations of the disease, do not have any degree of ductal dilatation[3]. They are not candidates for a drainage procedure since the normal diameter of the pancreatic duct is inadequate to ensure a patent anastomosis. Under these circumstances there is little alternative to pancreatectomy, which generally includes removal of adjacent viscera such as the terminal bile duct, duodenum and spleen[4]. If appreciable endocrine or exocrine function remains, partial resection is indicated with preservation of the more normal segment of the gland. Sometimes the extent and severity of disease or the failure of esser procedures necessitate complete extirpation of the pancreas, though few have much experience of the long-term consequences of this operation[5].

We present here a personal series of 30 patients undergoing some type of pancreatic resection for chronic pancreatitis over he last 8 years. Of these 22 had a partial resection, either proximal or distal, with removal of at least half the gland. Twelve received total pancreatoduodenectomy, including four with an unsuccessful distal resection.

Patients and methods

Clinical material

Between 1977 and 1984 in this unit, 30 patients with severe chronic pancreatitis underwent resection of 50 per cent or more of the pancreas. Six patients had a proximal pancreatectomy, sixteen had a distal pancreatectomy and twelve had a total pancreatectomy; four patients progressed from distal to total pancreatectomy (*Table 1*). There were 23 men and 7 women, with a mean age of 39 years at the time of operation (range 20–65 years). Thirteen patients were from the Bristol area, the remainder being referred from other centres in England and Wales or in one case from overseas.

During the same period 15 patients with chronic pancreatitis underwent some type of drainage operation without resection[6]. Another 14 patients, including 9 with the congenital anomaly of isolated dorsal pancreas (pancreas divisum), underwent a limited (20–40 per cent) distal pancreatectomy for suspected chronic pancreatitis[7]; changes of mild pancreatitis were confirmed histologically in 6 of the 14. Only the 30 patients undergoing major resections for severe disease are considered further in this paper.

Pre-operative investigations

These were undertaken to determine the severity and distribution of pancreatitis, the degree of pancreatic insufficiency and the presence of

Table 1 *Patients undergoing partial or total pancreatectomy*

	Distal pan-createctomy	Proximal pan-createctomy	Total pan-createctomy	Entire group
*n**	16	6	12	30
Male	12	3	11	23 (77%)
Mean age (years)	38	41	38	39
Mean duration of symptoms (years)	3·4	4·0	6·0	4·6
Previous pancreatobiliary surgery	5	1	11	13 (43%)
Calcification	9	5	9	20 (67%)
Pseudocyst	5	3	4	11 (37%)

* Four patients progressed from distal to total pancreatectomy.

complications such as pseudocyst, duodenal stenosis and splenic vein thrombosis. Pancreatic function tests were repeated postoperatively, and symptomatic review was carried out at a median of 4·5 years (range 1·5–9·5 years). Endocrine function was assessed by an oral glucose tolerance test, using a 50 g loading dose during the early years and 75 g latterly. Exocrine function was measured by one of more of the following: 3-day collection of faeces for estimation of fat content (N < 15 mmol/day), pancreolauryl test[8] (N > 30 per cent) and duodenal intubation studies using both secretin and a Lundh meal to stimulate the pancreas. Serum amylase was measured at least once, together with liver function tests and serum ethanol.

Pancreatic calcification was sought on plain abdominal radiographs supplemented by ultrasound and computed tomography scans, and X-ray of the resection specimens. Selective visceral angiography was performed in 16 patients with cannulation of both the coeliac axis and superior mesenteric artery; venous-phase films were routinely included. Every patient underwent endoscopic retrograde choledochopancreatography (ERCP) at some stage of their disease, eight patients on more than one occasion. In addition, operative pancreatography was carried out in 11 patients, generally by cannulation of the duct at the site of transection during partial pancreatectomy[9].

Results

Aetiology (Table 2)

Chronic alcoholism was the main aetiological agent in 19 of the 30 patients. Present for a minimum of 10 years, alcohol abuse was much more common among men, 17 of the 23 men being alcoholics but only 2 of the 7 women (74 per cent *versus* 29 per cent; $P = 0{\cdot}04$, χ^2 test). Alcohol also predominated in the group of patients with disease severe enough to warrant total pancreatectomy (all but one of whom were male). Eleven of the nineteen alcoholics had had acute exacerbations of pain associated with hyperamylasaemia. In seven non-alcoholic patients (including four women), one or more previous attacks of severe acute pancreatitis may have been the aetiological cause of subsequent chronic pancreatitis.

Presentation

Symptoms had been present for between 3 months and 17 years. The mean duration of symptoms was longer before total pancreatectomy (6·0 years) than partial pancreatectomy (3·5–4·0 years; $P = 0{\cdot}03$, Mann–Whitney U test) (*Table 1*). Similarly 11 of 12 total pancreatectomy patients had had between one and three previous operations on the pancreatobiliary tract as opposed to 6 of 22 partial pancreatectomy patients ($P = 0{\cdot}001$, χ^2 test).

Abdominal pain was the overwhelming symptom that demanded operative relief. Among the total pancreatectomy patients pain was always severe and unrelenting despite increasing doses of opiate analgesics. About half the partial pancreatectomy patients had a similar pattern of pain requiring regular analgesia; the remainder had mild continuous pain punctuated by episodes of severe pain lasting several days. Vomiting often accompanied severe attacks and three patients had duodenal stenosis. In 20 patients weight loss exceeded 10 kg. Four patients gave a history of jaundice and one had a left pleural effusion. Five patients had already had a chemical splanchnicectomy, one of them on six occasions.

Table 2 *Aetiological factors in chronic pancreatitis*†

	Distal pan-createctomy	Proximal pan-createctomy	Total pan-createctomy	Entire group
n*	16	6	12	30
Alcohol	8	4	9	19 (63%)
Acute pancreatitis	5	2	1	7 (23%)
Idiopathic	3	0	2	4 (13%)

* Four patients progressed from distal to total pancreatectomy
† Possible contributory factors were gallstones in four patients and congenital anomalies in two: annular pancreas in an alcoholic man of 43 years and multiple congenital cysts plus ductal ectasia in a man of 20 years without other aetiological factors

Table 3 *Endocrine and exocrine function before and immediately after pancreatic resection*

	Distal pan-createctomy ($n=16$)		Proximal pan-createctomy ($n=6$)		Total pan-createctomy ($n=12$)	
	Before	After	Before	After	Before	After
Endocrine function						
Normal	7	6	2	3	2	1
Glucose intolerance	9	6	4	3	3	0
Diabetic on insulin	0	4	0	0	7	11
Exocrine function						
Normal	6	6	1	0	0	0
Abnormal on testing	7	5	3	3	7	0
Steatorrhoea on enzymes	3	5	2	3	5	12

Although 13 of the 22 patients undergoing partial pancreatectomy (distal or proximal) had abnormal glucose tolerance, none were receiving insulin or oral hypoglycaemic agents (*Table 3*). Five had steatorrhoea with a pancreolauryl test value below 10 per cent, indicating near total exocrine failure. Pre-operative endocrine and exocrine function were much poorer in patients coming to total pancreatectomy, about half of whom were already on full replacement therapy.

Investigations

Calcification of the pancreas was detected in two-thirds of the patients (*Table 1*). Modest elevations in serum amylase were recorded in 10 patients during routine pre-operative testing; in another two with cystic disease the value exceeded 1000 units/l. Pseudocysts complicated chronic pancreatitis in 11 patients. Five cysts had been drained at a previous laparotomy, and the other six were included in the resection specimen.

Angiography showed few specific features. In two patients with a large cyst the vessels were clearly splayed around an avascular mass. In another three there was an abnormal vascular pattern in the region of the pancreatic head, raising the possibility of carcinoma. Unfortunately angiograms were not available in one patient with virtual occlusion of the portal vein or another two patients in whom arterial anomalies led to operative mishap.

ERCP was useful in confirming the diagnosis, indicating the distribution of chronic pancreatitis and helping to choose between resection and drainage. ERCP could not be performed in four patients, three of whom had duodenal stenosis; in the fourth, cannulation of the ampulla was unsuccessful and provoked an attack of acute pancreatitis. In another seven patients the examination was misleading, either because it suggested carcinoma or because it failed to demonstrate ductal ectasia in the body of the pancreas. Thus ERCP provided complete and accurate information about the ductal tree in 19 of 30 cases (63 per cent). In the remainder the gland had to be assessed or the assessment revised at laparotomy, sometimes supplemented by on-table pancreatography.

Operations and outcome

Distal pancreatectomy (Figure 1). This procedure was undertaken when disease appeared confined to the left pancreas (4 patients) or predominated in this region (12 patients). Eleven patients had hemipancreatectomy (50–60 per cent), while in five the resection was more extensive (70–80 per cent)[10]. In one case the body and tail of the pancreas had undergone sclerosis and shrinkage, exposing the splenic vein below the gland and facilitating a conservative (70 per cent) resection that preserved the spleen[11]; the extent of peripancreatitis generally prevented this manoeuvre. Transection through the neck of the pancreas in one man showed unexpected dilatation of the main duct, which was opened up for 6 cm; thus distal resection was combined with

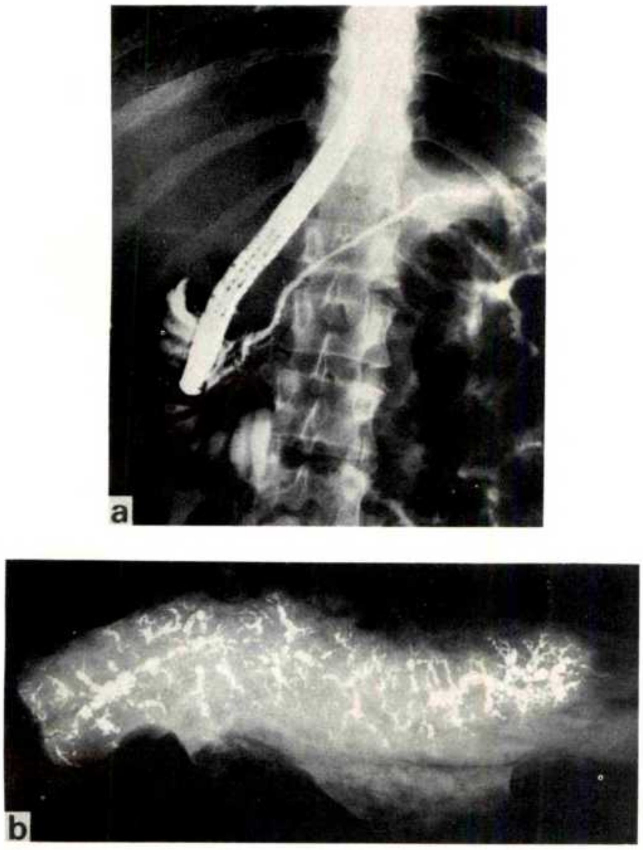

Figure 1 *Radiographs obtained from a 35-year-old woman submitted to 50 per cent distal pancreatectomy for chronic alcoholic pancreatitis.* **a**, *ERCP showing variable ductal calibre particularly in the pancreatic tail.* **b**, *An X-ray of the resection specimen revealing extensive pancreatic calcification of a ductal pattern*

Roux loop drainage of the proximal pancreas. In all other patients the duct was underrun and the amputated gland was oversewn with interrupted silk sutures. Three patients had an on-table coeliac plexus block with 30–40 ml of 50 per cent alcohol.

Particular difficulty was encountered during the dissection in two patients with densely adherent pseudocysts. In one case the superior mesenteric artery was inadvertently ligated and divided. The vessel was repaired at once by end-to-end anastomosis, and there were no untoward sequelae. In the second case the portal vein was torn, and in an attempt to expose the damage the neck of the pancreas was quickly divided together with the splenic artery, which took origin at a lower level than normal from a common coeliacomesenteric trunk; no angiogram was available. Although bleeding was controlled, subsequent laparotomy was needed for reactive haemorrhage. Fortunately residual pancreatectomy 2 years later proceeded more smoothly.

Two patients developed a collection of pancreatic juice in the lesser sac, one of which drained spontaneously. The other patient was discharged in good health but was readmitted 5 weeks postoperatively for percutaneous aspiration of a small collection. Shortly afterwards he sustained a massive pulmonary embolus from which he ultimately died despite emergency embolectomy. Notwithstanding the extent of resection exocrine function only deteriorated in two patients as a direct result of operation, although another five later required enzyme supplements as the disease progressed (*Table 3*). Endocrine function was essentially unaltered in nine patients, but in four operation exacerbated pre-existing glucose intolerance and insulin was needed. Continuing pancreatitis provoked late diabetes in another two patients.

The 15 survivors have been followed for a median of 5 years. Recurrence of severe pain has led to total residual pancreatectomy in four patients at 15–28 months. Another three patients had episodes of moderately severe pain now controlled by coeliac plexus blockade in two and by pancreatic sphincteroplasty at 5 years in the third. Of the remaining eight patients five have lasting pain relief, two need intermittent oral analgesics and one has more severe pain.

Proximal pancreatectomy. All six patients had diffuse pancreatitis with maximal changes in the head. One had an annular pancreas, one a large cyst and one obstructive jaundice. There was only one distal gastrectomy, the other five patients having conservative pylorus-preserving proximal pancreatoduodenectomy (PPPP)[11,12]. In three cases an ectatic duct was opened for 6–8 cm in the body of the pancreas, so that proximal resection was combined with distal drainage.

There were no intra-operative problems of note and no postoperative complications. Loss of the proximal half of the pancreas has not been associated with appreciable deterioration in endocrine function (*Table 3*); indeed, one jaundiced patient improved after PPPP. Operation precipitated exocrine failure in one, and in another steatorrhoea developed at 4 years because of progressive disease or late failure of the pancreatic anastomosis.

At follow-up (median 3·6 years) four patients have good pain relief while one requires frequent analgesia. The last patient required two coeliac plexus blocks for more severe pain but otherwise remained well for 5 years before two episodes of mesenteric venous thrombosis led to loss of nearly all the small intestine. Although she recovered from each episode and left hospital without parenteral nutrition, she gradually deteriorated and died of malnutrition 5·5 years after PPPP.

Total pancreatectomy (Figure 2). This operation was reserved for end-stage disease. Six patients had a one-stage total resection and six had resection of the residual head of pancreas after previous distal pancreatectomy in this unit ($n=4$) or elsewhere ($n=2$). Conventional pancreatoduodenectomy was carried out in eight patients with removal of one-third or one-half of the stomach; the other four had a conservative resection sparing the stomach and duodenal cap.

Mobilization of the pancreas was always laborious and sometimes hazardous. Median operative time was 6 h (range 5–8·5 h) and median blood loss was 4 units (range 3–21 units). In one man with an anomalous origin of the right hepatic artery the main superior mesenteric artery was transected and then re-anastomosed end-to-end; angiography had not been performed. In three patients the pancreas was so firmly adherent to the great veins that a small sliver of head and/or uncinate process was left *in situ* to avoid the risk of exsanguination. Quite remarkably, in one man this fragment sufficed to prevent diabetes for over a year. Lastly the transverse mesocolon could not be freed in one patient and transverse colectomy was carried out as well.

One patient became jaundiced immediately after operation and required revision of a tight biliary anastomosis at 8 days. There was one postoperative death in a man with three previous operations: cholecystectomy for empyema, choledochojejunostomy Roux-en-Y for bile duct stenosis and drainage of an infected pancreatic pseudocyst. He also had duodenal stenosis and partial occlusion of the portal vein. He collapsed and died at 8 days. Autopsy revealed venous gangrene of the previous Roux loop, which must have been compromised during mobilization of the head of pancreas.

Three other patients have subsequently died. A man of 57 years had a small coincident carcinoma in the neck of pancreas and died of carcinomatosis at 3 months. Another alcoholic aged 38 years died of diabetic ketoacidosis at 18 months. The third, a man of 34 years who continued to drink alcohol, was found dead at home 2·5 years postoperatively. Death probably resulted from hypoglycaemia, which may have been induced intentionally because of serious marital problems and depression. Three patients have had further laparotomy at a later stage, one

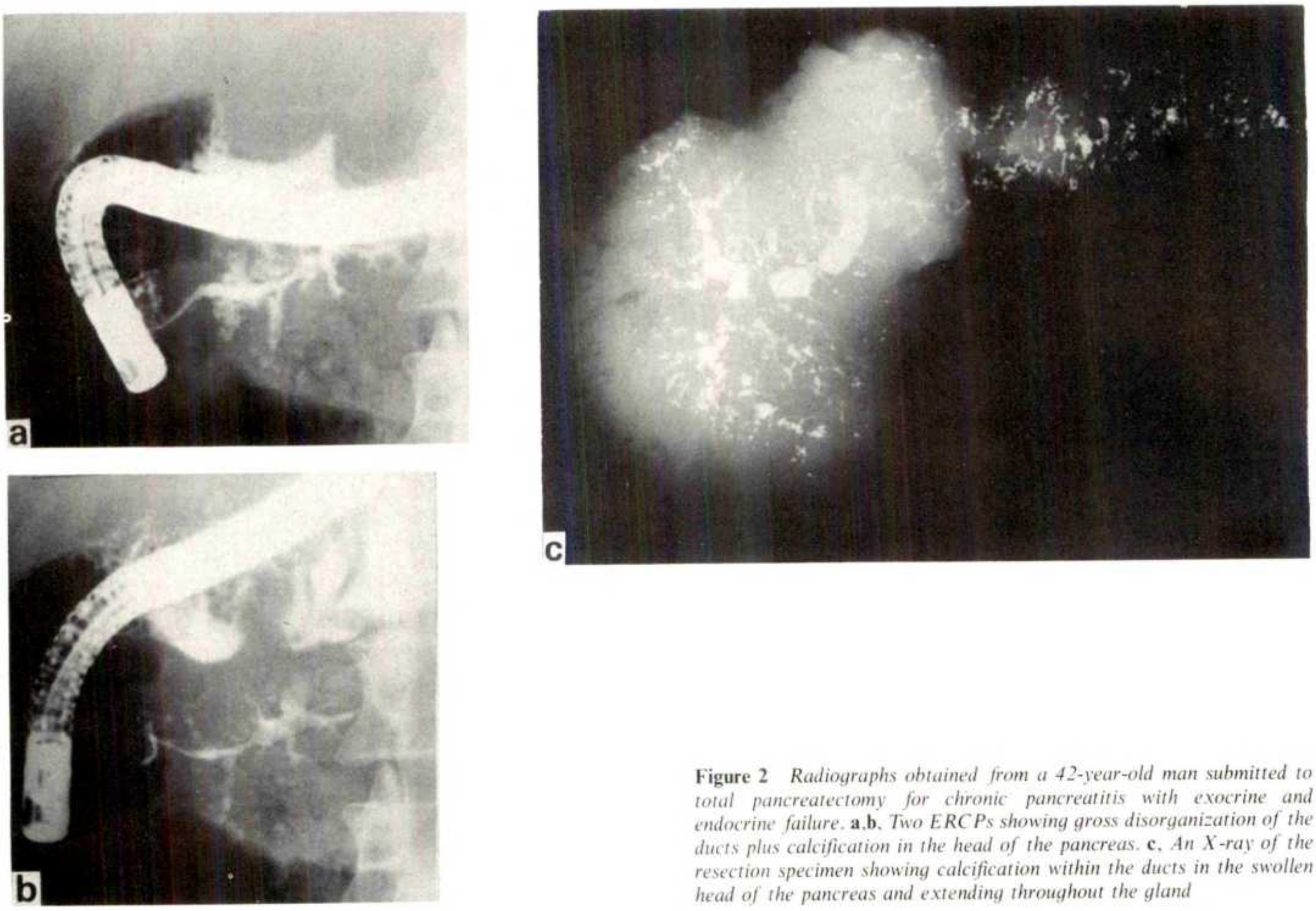

Figure 2 *Radiographs obtained from a 42-year-old man submitted to total pancreatectomy for chronic pancreatitis with exocrine and endocrine failure.* **a**,**b**, *Two ERCPs showing gross disorganization of the ducts plus calcification in the head of the pancreas.* **c**, *An X-ray of the resection specimen showing calcification within the ducts in the swollen head of the pancreas and extending throughout the gland*

for adhesion obstruction, one for peritonitis of uncertain cause and one for delayed gastric emptying 2 years after PPPP.

Management of exocrine and/or endocrine failure has been difficult in about half the survivors, but all have gained weight satisfactorily. Several patients require an H_2-receptor antagonist together with oral enzymes to suppress steatorrhoea. Diabetes has sometimes been brittle, and insulin requirements have ranged from 24 to 48 units/day. One alcoholic developed hypoglycaemia artefacta about 18 months postoperatively. It was conclusively shown that he was self-administering an excessive dose of insulin, presumably to attract attention. Fortunately this habit ceased and he remains well and painfree at 8 years. Another alcoholic developed a hepatic abscess at 7 years and survived two cardiac arrests and percutaneous aspiration.

Pain relief has been good in 7 of 10 patients surviving for a minimum of 18 months (median 4·5 years). The other three have continued to require regular analgesics. Only one of them has continued on opiates and he is the man whose tiny remnant of pancreas prevented diabetes.

Entire group (Table 4). The 30-day hospital mortality rate was 3 per cent. Another five patients (17 per cent) have died during the period of review, one of them from pulmonary embolism at 6 weeks. This patient and two others needed early reoperation for postoperative complications. Eleven patients (37 per cent) have needed late reoperation for a variety of causes, including completion pancreatectomy in four. In 27 patients pain relief was ultimately assessed 1·5–9·5 years after operation (median 4·5 years). Of these, 16 were almost completely free of pain, 8 needed non-opiate analgesics on a fairly regular basis and 3 had more severe pain. Among 10 patients suspected of continuing alcohol abuse there were only 3 with good pain relief. Lastly 8 patients required insulin and 10 patients required enzymes as a direct result of operation.

Table 4 *Outcome in patients undergoing pancreatic resection*

	Distal pan-createctomy	Proximal pan-createctomy	Total pan-createctomy	Entire group
n	16*	6	12	30
30-day deaths	0	0	1	1 (3%)
Postoperative complications	3	0	1	4 (12%)
Late deaths	1	1	3	5 (17%)
Late reoperation	7*	1	3	11 (37%)
Patients surviving 18 months	15	6	10	27 (90%)
Pain relief				
Good	5	4	7	16 (59%)
Fair	5	1	2	8 (30%)
Poor	5*	1	1	3 (11%)

* Includes four patients who subsequently progressed to total pancreatectomy

Discussion

The typical patient requiring pancreatectomy for chronic pancreatitis is a man in the fourth or fifth decade of life with a long history of alcohol abuse (*Table 5*)[3–5,13–18]. In this respect the Bristol patients are consistent with those reported from elsewhere in the world over the last 12 years, including the USA[3–5,14–16,18], France[13,17] and West Germany[19]. Only in Japan does the proportion of alcoholics drop below 50 per cent (to 30 per cent), though even here the disease predominates in men[20].

Pseudocysts were present in about a third of patients in this and other series[4,15,17]. Cysts magnify the operative risk, yet resection is more likely than simple drainage to avoid the chance

Table 5 *Pancreatectomy for chronic pancreatitis: comparison between series*

Authors	Study period (years)	No. of patients	Males (%)	Mean age (years)	Alcoholics (%)	Resection				30-day deaths (%)	Follow-up (years)	Poor result (%)
						Distal*	Subtotal†	Proximal	Total			
Leger *et al.* (1974)[13]	≈20	87	90	39	57	71	—	16	—	7	>5	27
Frey *et al.* (1976)[4]	21	149	68	40	79	53	77	19	4§	2	6–9	20
Braasch *et al.* (1978)[5]	25	26	62	47	58	—	—	—	26	0	4·1	37
Proctor *et al.* (1979)[14]	21	25	68	47	100	17	1	7	—	4	3·2	24
Traverso *et al.* (1979)[3]	22	28	53‡	44‡	65‡	7	8	5	8	11	3·2	24
White and Slavotinek (1979)[15]	19	30	50	41	60	16	9	5	2§	10	>6	27
Taylor *et al.* (1981)[16]	10	69	72	?	71	40		29	—	3	5	?
Moreaux (1984)[17]	14	50	100	42	100	—	—	50	—	2	>5	9
Morrow *et al.* (1984)[18]	10	39	72‡	46‡	56‡	21	18	—	—	5	>5	18
Present series (1986)	8	30	77	39	63	16	—	6	12§	3	4·5	11

* 40–80 per cent resection

† 80–95 per cent resection

‡ Data obtained from larger number of patients, not all of whom underwent resection

§ Including patients with previous partial pancreatectomy

of recurrent cyst formation or bleeding from eroded arteries in the wall[21]. Compression of the bile duct, duodenum or splenic vein are uncommon but clear-cut indications for operation in chronic pancreatitis. The incidence of pancreatic calcification in Bristol (67 per cent) exceeds that in all but Leger's series[13]; routine X-ray of the resection specimen refines the detection of fine calcification.

We have used ultrasound and CT scan in initial evaluation of the pancreas, supplemented by ERCP. Difficulty in obtaining or interpreting the endoscopic pancreatogram in 37 per cent of patients underlines the importance of examining the entire pancreas at operation and proceeding to on-table pancreatography if there is any likelihood of ductal ectasia[9]. Selective visceral angiography is an important prelude to any type of pancreatic resection. Although angiograms have a limited diagnostic role, they do provide invaluable information about ectopic arteries and distortion or compression of the great veins. Major vessels were damaged at operation in three patients, two of whom had unsuspected arterial anomalies.

The technical difficulties of pancreatic resection in chronic pancreatitis should not be underrated. Our one operative death followed total pancreatectomy, which is often performed after previous operations or nerve blocks have failed. The overall 30-day mortality rate of 3 per cent is well within the range of the other series listed in *Table 5* (0–11 per cent). In addition 10 per cent of patients needed early reoperation for reactive haemorrhage, biliary stricture or pulmonary embolus. Higher complication rates have often been described[4,14,16,17].

However logical, our attempts to tailor the extent of partial pancreatectomy to the distribution of pancreatitis were sometimes thwarted by progression of the disease. In particular the results of distal pancreatectomy were disappointing. Five of 15 survivors have needed further pancreatic surgery, all but one a completion pancreatectomy; after 5 years only a third have good pain relief. By contrast, pain has been abolished in four of six patients with proximal resection, diminished in a fifth and controlled in the sixth by repeat nerve blocks. Moreover, endocrine function was more likely to deteriorate after distal than proximal hemipancreatectomy, presumably because of the predominance of islets in the body and tail of the gland[22]. Although a distal resection of up to 75 per cent could sometimes be tolerated without the development of overt diabetes, four patients required insulin as a direct result of distal pancreatectomy and another two drifted into insulin dependence at a later stage. By contrast, none of the proximal pancreatectomy patients required treatment for glucose intolerance, though operation did precipitate exocrine failure in one of them. Proximal pancreatoduodenectomy is clearly a more major operation than distal pancreatectomy, yet the procedure was better tolerated in the present small series. Therefore, in patients with diffuse pancreatitis who retain some endocrine function, it may be better to remove the head of pancreas than the tail[3,17,19,23]. Others have found distal pancreatectomy equally unsatisfactory[13,15,16].

The ability of total pancreatectomy to control pain intractable by other means justifies its continued use in end-stage disease, especially where lesser procedures have failed or there is pre-existing pancreatic failure. Braasch has shown that the operation can be carried out with a zero mortality rate, though half his patients had serious postoperative complications, including sepsis, bile fistula and bleeding[5]. Our complication rate was lower, but several of our survivors have had problems with unstable diabetes, malabsorption or intercurrent illness. Nevertheless, only one patient has not had substantial pain relief from total pancreatectomy. We regard subtotal pancreatectomy, i.e. 80–95 per cent distal resection, as an unattractive alternative. Devascularization of the duodenum and bile duct injury are specific complications, diabetes is almost inevitable, yet pain relief is unreliable[4,24]; moreover, islet autotransplantation has yet to prove its value[18,25]. The operation of duodenum-preserving total pancreatectomy must still be regarded as experimental[26]. In selected cases we would therefore advocate total pancreatoduodenectomy, if possible by the pylorus-preserving technique[11,12,27] and if necessary leaving a small portion of tissue to protect the great veins[17,28].

Many authors report a disquieting incidence of late deaths (20–40 per cent) after any type of operation for chronic pancreatitis, especially among alcoholics who continue to drink[5,13,16,17,19,24]. Death can result from cirrhosis of the liver, suicide, hyper- or hypoglycaemic coma, myocardial infarction and carcinoma of the bronchus or pancreas. Our incidence of late death has been 17 per cent. Two patients died from venous thrombo-embolism and two from diabetic complications associated with continuing alcoholism. The fifth had concomitant carcinoma of the pancreas; White and Slavotinek report an 8 per cent incidence of this association[15]. One conclusion is unavoidable: patients with little or no residual pancreas need vigilant management for the rest of their lives.

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Surgical treatment of pancreatic pseudocysts

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Between 1966 and 1980, 54 patients (40 men and 14 women) with a mean age of 38 years were operated on for a pancreatic pseudocyst at the Department of General Surgery, University of Göttingen. The aetiology of the cysts was alcohol abuse in 35 patients, biliary diseases in 8, blunt abdominal trauma in 4, virus-induced in 2 and unknown in 5. With the exception of those who had had trauma, all patients were suffering from chronic pancreatitis. Surgical therapy included in all cases a cystojejunostomy (52 with a Roux-Y-limb and 2 with an omega loop). The mean follow-up period was 13 years (range 6 to 20 years). The late mortality was 15 per cent (8 of 52 patients). Recurrent cysts occurred in two patients (5 per cent) and relapse of pancreatitis in one third of the patients. Deterioration of carbohydrate metabolism was observed in 20 per cent of the patients. After drainage operation stool fat content became normal in 20 per cent and deteriorated in 13 per cent. Persistence or cessation of alcohol intake influenced the long-term results. From these data we conclude that both alcohol withdrawal and sufficient drainage of the pseudocyst are important factors in the prognosis of pseudocyst.

Keywords: Pancreatic pseudocysts, chronic pancreatitis, internal drainage, long-term results.

Pancreatic pseudocysts are most commonly associated with inflammatory diseases of the pancreas, usually caused by alcoholic abuse or biliary diseases[1–4]. Pseudocysts have been recognized more frequently in Europe in the last decade, probably due to increasing alcohol consumption and the advent of diagnostic management. The development of ultrasonography and computerized tomographic scanning (CT) has provided non-invasive and accurate methods for detecting pancreatic pseudocysts[2–5].

Although there is general agreement in the literature that the best treatment of pseudocysts is internal drainage[3,5–11] little is known of the long-term results of this procedure. The purpose of this study was to review the follow-up results of internal drainage of pancreatic pseudocysts in a group of patients mostly suffering from chronic pancreatitis in order to assess whether internal drainage had improved their quality of life and/or preserved their pancreatic function.

Patients and methods

Between 1966 and 1980, 54 patients (40 men and 14 women) with a mean age of 38 years (range 29–67) were operated on for a pancreatic pseudocyst at the Department of General Surgery at Göttingen University. The probable aetiology, age and sex distribution are shown in *Table 1*. Most of the patients were suffering from chronic pancreatitis. Up to 1978 diagnosis of the pseudocysts was made by conventional radiographic contrast studies, such as barium meal, amylase determination and clinical signs. Since 1978 ultrasonography, CT and endoscopic retrograde cholangiopancreaticography (ERCP) have become available as a routine basis to evaluate pseudocysts. Most of the cysts (49) were intrapancreatic with a mean diameter of 7 cm (range 5–10 cm). Cysts were mostly localized in the head of the pancreas (33), in the neck (12) and in the body (9). In the 39 cases with operative cystography, 21 cysts were found to communicate with the duct of Wirsung, and 18 did not. In five patients with chronic pancreatitis of alcoholic aetiology, pseudocysts developed in an acute attack of pancreatitis.

Indications for surgical treatment were abdominal pain, $n=52$; palpable mass in the upper abdomen, $n=39$; stenosis of the duodenum, $n=23$; duration of the cysts for more than 6 weeks, $n=54$; and pleural effusion, $n=4$. All patients were treated by internal drainage with a cystojejunostomy: 52 with a Roux-Y-limb and 2 with an omega loop. Cystojejunostomy was performed because most of the cysts were large and not adherent to the stomach.

Follow-up studies were performed in 42 of the 54 patients after operation. Two patients died within 28 days, resulting in a postoperative mortality rate of 3·7 per cent. The remaining 10 patients have died or been lost to follow-up. The postoperative condition of the 42 patients was evaluated either by rehospitalization or by enquiries of the patients and their families or their physicians. Patients who had died were assessed by review and autopsy findings when available, and relatives were contacted whenever possible to evaluate the therapeutic results of the operations.

The following parameters were evaluated for assessment of the result: late mortality, general condition, pain relief, changes in body weight, endocrine function of the pancreas, exocrine function of the pancreas, relapses of pancreatitis and recurrence of pseudocysts.

The time since operation and follow-up varied from 6 to 20 years, with a mean of 13 years.

Results

Late mortality rate (Table 2)

The late mortality rate was 15 per cent (8 of 52 patients). The mean survival time was 4·3 years. Five of the eight patients died within the first 5 years. From the seventh postoperative year onwards the rate of survival remained stable. Abstinence from alcohol affected survival, as those alcoholic patients who died had not stopped drinking, and the cause of death in six of eight cases was directly induced by alcohol abuse (two patients died of necrotizing pancreatitis, three of liver cirrhosis and one of bleeding oesophageal varices).

Table 1 *Aetiology, age and sex distribution in 54 patients with pancreatic pseudocysts*

Aetiology	*n*	%	Age	Male	Female
Alcohol	35	65	33 ± 4	29	6
Biliary disease	8	15	51 ± 5	2	6
Trauma	4	7·4	41 ± 3	4	
Virus-induced?	2	3·7	27 ± 3	2	
Unknown	5	9·2	63 ± 4	3	2

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Table 2 *General condition, pain relief and changes in body weight in 42 patients after cyst drainage*

	n	(%)
General condition		
Good	22	(52)
Fair	7	(17)
Poor	13	(31)
Pain relief		
Good	13	(31)
Fair	11	(26)
Poor	18	(43)
Changes in body weight		
Gained	17	(40)
Unchanged	10	(24)
Lost	15	(36)

General condition, pain relief and change in body weight (Table 2)

Pre-operatively all patients were severely restricted by their disease with frequent time off work. Postoperatively the majority felt fit again. The classification 'good' indicates that the general condition and fitness for work was improved and the patient had resumed normal activity. 'Fair' means that the patient was improved but remained slightly impaired and needed continued treatment. 'Poor' indicates that there was no change in general condition and the patient remained under medical treatment because of complications. Cyst drainage was associated with improvement in 29 patients (69 per cent) and poor results in 13 cases (31 per cent). Nearly 80 per cent of the patients continued to work sometimes in spite of continuing symptoms. In eight cases (19 per cent) work was not restarted after operation.

Abdominal pain was the cardinal feature in all cases. The effect of operation on pain was carefully surveyed in the surviving 42 patients. Pain relief was obtained in 13 patients (31 per cent), 11 patients had satisfactory results (26 per cent) and in 18 cases (43 per cent) pain recurred. Among the non-alcoholic group nearly all patients were completely free of pain.

Pre-operatively 30 of 42 patients were underweight, 6 had a normal and 6 an ideal body weight. Cyst drainage caused weight gain in 17 cases (40 per cent), the body weight was unchanged in 10 patients (24 per cent) and fell in 15 cases (36 per cent). However, the majority remained slim, maintained their weight or had a progressive loss. Some of the patients whose weight had decreased were found to have incorrect dietary habits or insufficient enzyme correction.

Endocrine function of the pancreas

A comparison of pre- and postoperative glucose tolerance test was possible in 29 patients. Endocrine function after cyst drainage remained unimpaired in 34 patients (81 per cent) and deteriorated in 6 (14 per cent), as determined by the glucose tolerance test. Two patients developed an insulin-requiring diabetes. Improvement of the glucose tolerance test was achieved in two patients. Control of diabetes was difficult in patients who continued drinking alcohol.

Exocrine function of the pancreas

Digestive function was assessed by the presence of steatorrhoea and stool fat determinations. Pre- and postoperative secretin-pancreozymin tests under the same condition were performed in 17 patients. Determination of faecal fat was performed in a 72-h stool collection in the absence of enzyme substitution for at least 3 days before the tests. The mean fat content in the meal was 100 g/day. The secretin-pancreozymin test was performed according to the method described by Lankisch *et al.*[12]. After drainage operation stool fat content became normal in eight patients (19 per cent) but abnormal in five (12 per cent). The secretin-pancreozymin test had improved in eight patients (47 per cent), not changed in five (29 per cent) and deteriorated in four cases (24 per cent).

Relapses of pancreatitis

One third of our group developed attacks of pancreatitis after surgery. Most of these were alcoholics and had not stopped drinking. All required hospital admission.

In five, acute pancreatitis was of slight or moderate severity, however nine patients had severe complications such as shock, respiratory and renal failure. Two patients died of necrotizing pancreatitis. The frequency of attack was in four cases up to three times.

Recurrent cysts

Two patients (5 per cent) developed a further pseudocyst after cystojejunostomy. The recurrent cysts were diagnosed by clinical signs and CT and were found 2 and 7 years after operation. In both cases re-operation was not necessary, since the patients were treated by percutaneous drainage with a pigtail catheter for 7 and 9 weeks. The clinical presentation of the cyst was abdominal pain and a palpable mass in one case. Diagnosis was verified by ultrasound scanning and CT.

Influence of further alcohol consumption on long-term results (Table 3)

Persistence or cessation of alcohol intake obviously played an important role in functional results and survival rate as shown in *Table 3*. The average daily consumption of alcohol was 60 g. Most patients tended to consume alcohol daily. The preferred type of alcoholic beverage was beer.

Discussion

As the result of increasing alcohol consumption the incidence of inflammatory diseases of the pancreas and attendant pseudocysts is rising[1,3,8,11,13]. Many pseudocysts occur in the setting of chronic pancreatitis from duct obstruction and parenchymal fibrosis[1–3,7,8], but they may also result in the aftermath of acute pancreatitis from a process of autodigestion[2,8,14]. Because of the risk of secondary complications, such as haemorrhage, infection or spontaneous rupture most authors recommend drainage when a pseudocyst persists after 6–8 weeks of conservative treatment as it is unlikely to resolve after this period of time[8,15,16] and its wall is thick enough to allow internal drainage[13,17,18].

In our study we present a group of patients suffering from chronic pancreatitis, mostly of alcoholic aetiology, who were followed up for a mean of 13 years after cystojejunostomy. The percentage of alcoholics (65 per cent) was similar to that in the series of McConnell *et al.*[7] but higher than in other reports[5,11,13]; in the study by Van Heerden and Remine[17] only 14 per cent were drinkers.

In nearly all cases an internal drainage with a Roux-Y-limb was performed. The cysts were mostly localized in the head and the body of the pancreas, which is in accordance with the intraoperative findings of Shatney and Lillehei[13].

Table 3 *Influence of further alcohol consumption on postoperative results of cyst drainage for pancreatic pseudocysts of alcoholic aetiology* (n = *21 patients*)

	Persistent alcohol intake ($n=12$)		Stopped drinking ($n=9$)	
Late mortality	4	(33)	1	(11)
General condition and pain relief 'good + fair'	3	(25)	6	(67)
Deteriorated endocrine and exocrine function	3	(25)	1	(11)
Relapses of pancreatitis	8	(67)	3	(33)

Values in parentheses are percentages

Late mortality in our study was 15 per cent. Coinciding with the experience of others[7,13,19] most of the patients died during the first few years after operation. Continued drinking was the main cause of late death, again in accordance with other reports[1,6,10,13]. Survival rates in those patients who did not stop drinking were significantly poorer than in those who continued to drink.

Our follow-up examination showed that the majority of patients (nearly 70 per cent) had done well or satisfactorily postoperatively, with improvement in their general condition and a return to work. Van Heerden and Remine[17] observed excellent results in 86 per cent of patients after internal drainage, but only 14 per cent of their cases had an alcoholic scrutiny and the mean follow-up period was only 7·8 years. In a 4 year follow-up Bødker *et al.*[10] reported that 45 per cent of their patients were free of pain. Although internal drainage of the pseudocyst usually will result in resolution of the cyst, persistence of recurrent pain is common. In our group nearly half of the patients reported persisting pain after surgery. In a review by Rossi *et al.*[20] only 25 per cent of patients were free of pain after cyst drainage. The cause of these disappointing results is obviously the underlying chronic pancreatitis with its irreversible morphological changes[1]. We now perform ERCP some hours before surgery to assess the pancreatic ductal system in patients with pseudocysts and chronic pancreatitis. By this method we can identify those patients who are candidates for more detailed treatment, such as concomitant drainage of a dilated duct system or a partial resection of the gland.

As an aspect of the underlying chronic pancreatitis we furthermore observed a high rate of attacks of acute pancreatitis after cyst drainage (33 per cent) which is also in agreement with other authors[8,19,20]. Persisting or recurring cysts were seen in 2 of 42 patients (5 per cent), which is similar to the findings of Mitty *et al.*[21] who reported from the literature a recurrence rate of 6 per cent in 365 cases after cystojejunostomy. McConnell *et al.* observed a recurrence rate of 7 per cent in patients with chronic pancreatitis[7].

Neither of our patients with recurrence required further surgery, but were treated by percutaneous drainage. Although our experience of percutaneous drainage of a recurrent cyst is rare, we suggest this method may offer an alternative to relaparotomy. However, we consider that percutaneous drainage of a cyst for more than 8 weeks is not useful and patients then should require surgery. Gerzof *et al.*[22] reported 11 pseudocysts that were drained in patients with pseudocyst infection. Although the method was used primarily to prepare patients for elective surgery, only 2 of 11 cysts recurred. Complications were minimal and usually followed when the catheter became occluded.

Information about endocrine function after cyst drainage is limited. The study shows that in rare cases this procedure can improve carbohydrate metabolism. We observed improvement of the glucose tolerance test in one patient with a post-traumatic cyst and one with chronic alcoholic pancreatitis. These findings may be due to an improvement in pancreatic juice drainage after decompressing the gland and perhaps to recovery of the inflamed gland. However, in the majority the endocrine function of the pancreas remained unimpaired and in 20 per cent glucose tolerance test deteriorated. Since this type of operation does not alter or eliminate islet cell mass we suggest that deterioration of endocrine function may be related to the natural progression of the inflammatory disease, which includes the destruction of islet cells[23,24].

Likewise, little is known about exocrine pancreatic function after drainage operations. In some cases improvement or even normal pancreatic function has been observed, which may be due to subsequent recovery of the gland or improvement in duct drainage. Following pancreatic trauma a gradual improvement of pancreatic function has been shown[24]. However, whether or not progressive deterioration of pancreatic function can be positively influenced by operation is primilarly dependent on the pre-operative function. Long-term results of cyst drainage are dependent on the cause of origin of the cyst. The diverse forms of pancreatitis resulting from alcohol, gallstones and trauma have to be differentiated. Furthermore, early results of the first 2 or 3 years cannot be compared with later results after more than 5 or 10 years.

It must also be remembered that drainage of a pseudocyst in chronic pancreatitis does not halt progression of the underlying disease. The success of cyst drainage is to a considerable extent dependent on the ability of alcoholic patients to withdraw from alcohol and on the pre-operative function of the pancreas. The prognostic importance of alcoholism and further consumption of alcohol has to be emphasized.

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Management of periampullary carcinoma

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Forty-one patients presented to our hospital between 1959 and 1983 with periampullary carcinoma. Twenty-six (63 per cent) underwent radical surgery, eight (20 per cent) local excision of the tumour, six (15 per cent) had bypass procedures and one was treated by endoscopic sphincterotomy (2 per cent). Potentially curative resection was performed in 83 per cent of the 41 patients. The operative mortalities for radical, local and bypass surgery were 7·7 per cent, 25 per cent and 16·6 per cent respectively. The degree of tumour differentiation significantly affected survival while local spread did not significantly affect survival in patients treated radically. The 5 year survival rates (calculated actuarially) for radical, local and bypass surgery were 34, 44 and 0 per cent respectively.

Keywords: Periampullary carcinoma, radical and local exicision

Periampullary cancer is an uncommon lesion which may comprise cells of differing origin. The tumour arises at or within 1 cm of the papilla of Vater with the cancer stemming from cells on the papilla or from nearby duodenal, common bile duct or pancreatic duct mucosa. A range of clinical behaviour is possible and few large series have been published. This paper presents the results of surgical treatment in a series of 41 patients dealt within one hospital.

Patients and methods

In the period 1 January 1959 to 31 December 1983, 50 patients admitted to Glasgow Royal Infirmary were diagnosed as having periampullary carcinoma, i.e. neoplasms developing at or within 1 cm of the papilla of Vater. In 41 of these patients the diagnosis was confirmed histologically during life. In two patients carcinoma was diagnosed at post-mortem while in five cases a bypass procedure was performed without biopsy of the lesion. The remaining two patients were found to have true neoplastic adenomatous polyps.

Only the 41 patients with periampullary carcinomas confirmed histologically during life are considered further in this retrospective study. There were 25 men (61 per cent) and 16 women (39 per cent) with median ages of 59 years (range 28–80) and 60·5 years (range 37–72) respectively. The age distribution in decades is shown in *Figure 1*.

Twenty-four of the patients (59 per cent) presented initially to this hospital, the rest being referred from other hospitals. Thirty-eight patients were or had recently been jaundiced (93 per cent) while three patients had apparently remained anicteric. Pain was reported by 19 patients (47 per cent); six of whom presented with acute pancreatitis as determined by hyperamylasaemia (> 1000 IU/l) and a consistent clinical picture. Three other patients had hyperamylasaemia (serum amylase between 300–1000 IU/l) but no other features to support a diagnosis of acute pancreatitis. Of the 41 patients 26 (63 per cent) underwent radical surgery (16 men, 10 women, median age 59 years, range 28–72), 8 (20 per cent) had local excision of the tumour (3 men, 5 women, median age 62 years, range 37–74) and 6 (15 per cent) had bypass procedures (5 men, 1 woman, median age 67 years, range 39–80). One male patient aged 76 was treated palliatively by endoscopic sphincterotomy to relieve obstructive jaundice.

Tumours were classified histologically from the initial pathology report as well differentiated, moderately well differentiated or poorly differentiated. Local invasion was regarded as invasion through serosa with or without invasion of lymphatics, blood vessels, lymph nodes or surrounding tissues or organs.

Cause of death has been established from a combination of post-mortem findings, hospital case notes and/or death certificates. Survival times have been calculated from the date of (first) surgery. Survival rates have been defined using standard life table methods[1]. Operative deaths (within 30 days of surgery) have been excluded from calculation of long-term survival rates. Calculation of the statistical significance of differences between survival curves was based on the log rank test[2]. When more than two survival curves have been compared, an overall *P* value was first calculated. If this was significant, pairwise comparisons were then carried out. The χ^2 and Fisher's exact tests have been used to compare the significance of differences between groups.

Results

Surgery and survival

The overall operative mortality rate for the whole group was 12 per cent with a 5 year survival rate of 29 per cent.

The 26 radical operations were performed by eight surgeons and consisted of 25 pancreaticoduodenectomies (Whipple procedures) and 1 total pancreatectomy. Of these operations 13 were performed as a single-stage procedure and 13 as a two-stage procedure with initial biliary decompression by cholecystjejunostomy (5 patients), cholecystduodenostomy (3 patients) or T tube drainage (5 patients). In one patient in whom the referring surgeon had failed to make the diagnosis at operation, bouginage of the lower end of the common bile duct had been performed followed by T tube drainage. There were two operative deaths in patients undergoing radical surgery (7·7 per cent); one from the single-stage group and one in the two-stage group. Both patients died within 48 h of surgery, one from respiratory failure and the other from a myocardial infarction. The median survival following radical surgery was 48 months (range 2–204). The median survival for patients

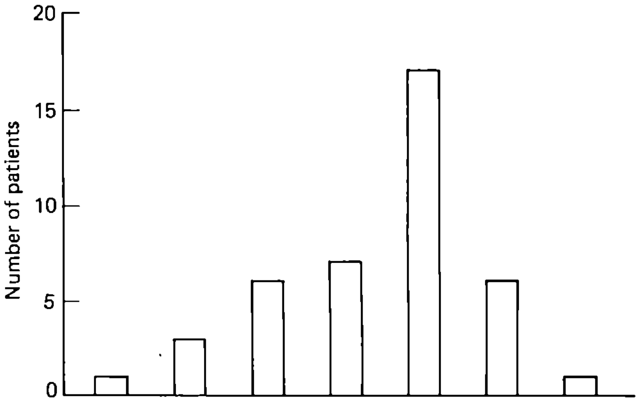

Figure 1 *Age distribution in decades of 41 patients with periampullary carcinoma*

undergoing one stage resection was 24 months (2–204) and after two-stage resection it was 54 months (10–165); this difference was not statistically significant. Survival calculated actuarially for patients undergoing radical surgery was 62 per cent at two years and 34 per cent at 5 years (*Figure 2*).

There were two operative deaths (25 per cent) in the eight patients who had local excision of their tumours. One patient died from a cerebrovascular accident 4 days after surgery and the other from acute pancreatitis and bronchopneumonia 1 week postoperatively. The eight local excisions were performed by five surgeons. Re-implantation of the common bile duct and pancreatic duct into the duodenum was performed in one of these eight. The median survival of the group was 57 months (range 3–71). The actuarial survival was 67 per cent at 2 years and 44 per cent at 5 years (*Figure 2*).

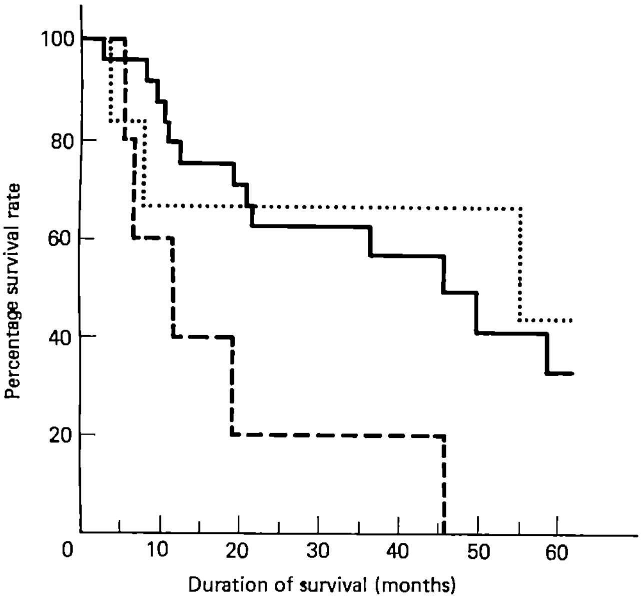

Figure 2 *Type of operation and actuarial survival rates in 35 patients with periampullary carcinoma who survived operation. Local excision · · ·, n=6; radical ——, n=24; bypass – – –, n=5. Survival of patients undergoing radical surgery is significantly greater than those undergoing bypass procedures.* $P<0\cdot05$

Table 1 *Cause of death following radical surgery and local excision for periampullary carcinoma*

	Cause of subsequent death				
Type of surgery	Operative mortality	Recurrent carcinoma	Intercurrent disease	Unknown	Patients still alive
Radical surgery ($n=26$)	2	10	4	1	9
Local excision ($n=8$)	2	3	2	—	1

The bypass procedures comprised four cholecystjejunostomies, one cholecystduodenostomy and one choledochoduodenostomy. One patient died after 3 weeks. The median survival was 10 months (range 3–45). The actuarial survival was 20 and 0 per cent at 2 and 5 years respectively. The longest survivor lived for 3 years after surgery. The remaining 76-year old patient with severe respiratory disease and ultrasound scan evidence of metastases had sphincterotomy following endoscopic retrograde cholangiopancreatography (ERCP) and biopsy. He died anicteric 2 months later from carcinomatosis secondary to his periampullary carcinoma.

There was a significant difference in survival ($P<0\cdot05$) between patients undergoing radical surgery and bypass surgery (*Figure 2*) but not between those having radical surgery as opposed to local excision. In all, 34 patients underwent potentially curative surgery (i.e. radical or local excision). Four died within 30 days of surgery but 10 of these patients are still alive. The cause of death in the remaining 20 is shown in *Table 1*; 13 patients (65 per cent) died from recurrent disease.

Histology and survival

All 41 patients had adenocarcinomas. There was no obvious difference between the three histological groups with regard to the type of operations performed (*Table 2*). Survival was significantly greater in patients with well differentiated tumours compared to those with poorly differentiated tumours ($P<0\cdot05$).

Each type of surgery was examined separately with regard to the degree of differentiation of the tumours. Only in the group undergoing radical surgery were there sufficient numbers to allow comparison (*Table 3*). After radical surgery survival was statistically greater ($P<0\cdot05$) in patients with well differentiated as opposed to poorly differentiated tumours, the actuarial survival being respectively 72 and 20 per cent at 2 years and 48 and 0 per cent at 5 years (*Figure 3*). The median survival for the three groups with decreasing degree of differentiation was 59, 42 and 10 months (*Table 3*).

Table 3 *Median survival (months) in relation to differentiation of the tumour and the type of operation*

	Operation		
Degree of differentiation	Radical surgery	Local excision	Bypass surgery
Well ($n=15$)	59 (11–204) ($n=11$)	60 (7–71) ($n=4$)	— ($n=0$)
Moderately well ($n=10$)	42 (7–164) ($n=8$)	— ($n=0$)	12 (6–18) ($n=2$)
Poor ($n=10$)	10 (2–57) ($n=5$)	5 (3–7) ($n=2$)	9 (5–19) ($n=3$)

Survival in months given as median value with range, $n=$number of patients in each group. Survival of patients with well differentiated tumours undergoing radical surgery is significantly longer than patients with poorly differentiated tumours ($P<0\cdot05$)

Table 2 *Tumour differentiation and median survival (months) in patients with periampullary carcinoma*

			Type of operation performed in 36 patients				
Degree of differentiation	Number of patients	Operative deaths	Radical surgery	Local excision	Bypass	Sphincterotomy	Median survival in months (excluding operative deaths)
Well	17	2	11	4	—	—	60
Moderately well	14	3	8	—	2	1	29
Poor*	10	0	5*	2	3	—	9

* Includes one anaplastic carcinoma. Survival of patients with well differentiated tumours is significantly longer than poorly differentiated ($P<0\cdot05$)

Local invasion and survival

Local invasion was regarded as invasion through serosa plus or minus invasion of lymphatics, blood vessels, lymph nodes or surrounding tissues or organs. Excluding the operative mortalities and the sphincterotomy, there was information regarding spread in 29 of the remaining 35 cases. No statistical difference could be shown between the two groups with regard to radical surgery, potentially curvative surgery (radical plus local excision) or when all three types of surgery were taken together (*Table 4*). In the largest group of patients (radical surgery) data are available in 20 patients regarding local invasion (*Figure 4*). This shows a trend towards better survival in patients without local invasion, but the total numbers and survival trends preclude a significance rating for this difference.

Discussion

Periampullary carcinoma is an uncommon neoplasm. This series and that reported by Schlippert *et al.*[3] show that its peak incidence is in the seventh decade. In common with most authors we found no clear sex predilection or any difference in age between the sexes[4–6], although Fish and Cleveland[7] claim that the tumour is more common in men. Jaundice and abdominal pain were the most common symptoms in our patients, a finding documented previously in a number of series[8–12]. The classical description of patients with periampullary tumours presenting with painless, sometimes fluctuating jaundice was found in only a minority of our patients. Six patients in our series presented with acute pancreatitis, an observation that has been separately reported in detail[13].

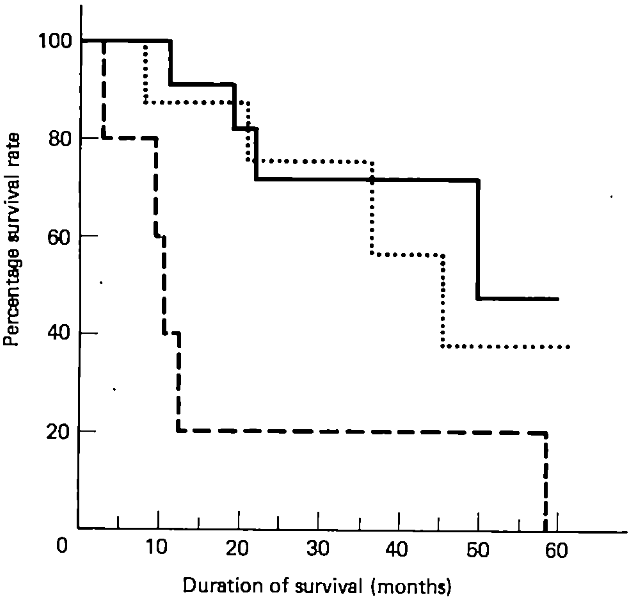

Figure 3 *Tumour differentiation and actuarial survival in 24 patients with periampullary carcinoma who survived radical surgery. Well differentiated* ———, n = *11; moderately well differentiated* ·····, n = *8; poorly differentiated* – – –, n = *5. Survival is significantly greater in patients with well differentiated tumours relative to those with poorly differentiated tumours*

The median age of patients undergoing radical surgery, local excision and bypass procedures rose progressively. Although this difference was not significant a similar trend was reported by Schlippert *et al.*[3] who suggested that it reflected a desire to avoid radical surgery in elderly, poor risk patients. Our operative mortality rate of 7·7 per cent for radical surgery compares favourably with that of other series[3–5,14], and was lower than the mortality following local excision (25 per cent) or bypass (16·6 per cent). Mortality rates were identical in patients undergoing single stage and two stage resections, in keeping with the experience of Akwari *et al.*[5]. Wise *et al.*[14] collected data from 31 series on 2390 reported cases of pancreaticoduodenectomy for periampullary cancer and on 138 cases of

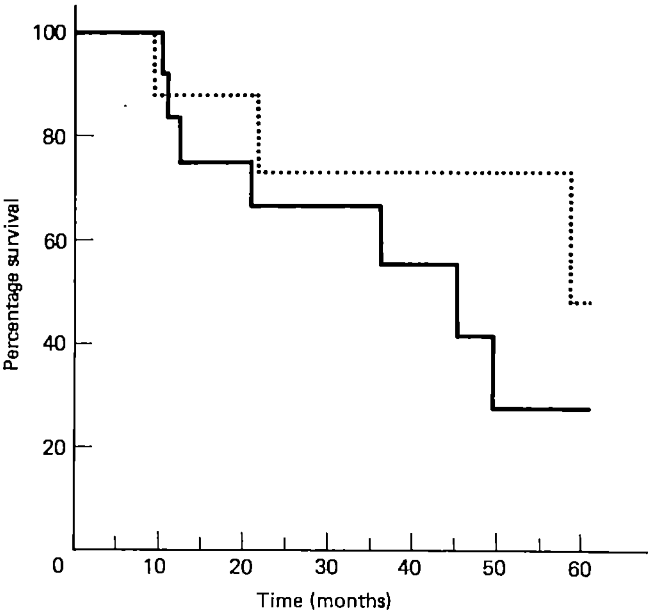

Figure 4 *Effect of local invasion on survival within the group of patients subjected to radical surgery. No invasion* ·····, n = *8; invasion* ———, n = *12*

Table 4 *Local invasion and survival (in 29 of the 35 patients who survived for more than 30 days after surgery)*

Operation	Number of patients	Survival (%) *n* years after surgery					Median survival (months)	*P*
		1	2	3	4	5		
Radical								
Spread	12	83	67	57	44	30	43	0·40
No spread	8	88	74	74	74	49	59	
Local excision								
Spread	4	50	50	50	50	50	> 60	
No spread	0	0	0	0	0	0		
Bypass								
Spread	4	50	25	25	0	0	12	
No spread	1	0	0	0	0	0		
Radical + local excision								
Spread	16	75	62	54	44	33	41	0·26
No spread	8	88	74	74	74	49	59	
All patients								
Spread	20	70	54	48	34	25	33	0·34
No spread	9	78	66	66	66	44	57	

transduodenal excision; the overall mortality rates were 18·8 and 27·5 per cent respectively. However, a recent review of ampullary carcinoma in north-west England reported no operative mortality following local excision and a subsequent 5 year survival rate of 51 per cent[15]. Radical surgery had a 30 per cent operative mortality with a 28 per cent 5 year survival rate. The cumulative mortality for local excision and radical surgery falls at similar rates in Knox and Kingston's series, the high operative mortality with radical surgery giving a false impression of a much poorer prognosis[15]. No less than 33 surgeons were involved in the treatment of these 61 patients.

Schlippert *et al.*[3] reported on 57 patients. Their series was comparable with our own in terms of the number of patients in each group; 31 underwent radical surgery, 7 had local excision of the tumour and 16 had bypass operations. The respective 5 year survival rates were 10, 17 and 0 per cent compared to 34, 44 and 0 per cent in our own series. There was no statistical difference between the survival after radical surgery and local excision. However, the higher 5 year survival following local excision in these two series was also noted by Wise *et al.*[14] and Knox and Kingston[15]. Local excision is therefore a reasonable approach to treatment. The survival rate after bypass surgery in our patients was particularly poor, all of the patients failing to live 4 years after surgery.

Endoscopic sphincterotomy was used in only one of our patients and gave good palliation in an elderly jaundiced man known to have disseminated disease. It has also been recommended for carrying out biliary decompression before definitive surgery[16,17]. In the past, opinion has been divided as to the merits of a one-stage or two-stage operation, although in our own series there was no difference either in operative mortality or survival. However, endoscopic sphincterotomy appears to overcome the major disadvantage of biliary decompression at laparotomy which often resulted in the second-stage operation being technically more difficult. Endoscopic sphincterotomy with or without stenting would seem to have a place both in palliation and in biliary decompression prior to definitive/curvative surgery.

Improved survival in patients with well differentiated tumours may be influenced by the fact that three of ten patients with poorly differentiated tumours were only considered suitable for bypass surgery while all 17 patients with well differentiated tumours had potentially curative surgery. In patients undergoing radical surgery survival was again significantly greater in patients with well differentiated tumours. Local invasion did not significantly affect survival in our series.

The majority of patients in this series were primary referrals suggesting that the spectrum of patients is a representative cross section of those developing periampullary carcinoma. Potentially curative resections were performed in 83 per cent of the 41 patients. Despite this high 'curative' resection rate the overall 5 year survival was only 29 per cent. Following radical surgery the 5 year survival was 34 per cent. This is identical with the figure cited by Akwari *et al.*[5] which is better than that of most other series[6-8,18,20-24] but poorer than some[9,19,25]. Knox and Kingston[15] support the case for local excision of periampullary carcinoma, but their mortality for radical surgery was four times greater than our own. We feel unable to recommend local excision, in view of the problems encountered, except in older, higher risk patients unfit for major surgery. Provided that pancreaticoduodenectomy can be performed safely it should still be regarded as the operation of choice until there is unequivocal evidence to support the case for local excision. Preservation of the pylorus is becoming an increasingly popular modification of the traditional operation of pancreaticoduodenectomy and we see no reason to remove the pylorus routinely, provided its retention does not compromise the extent of resection.

Acknowledgements

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Surgical workshop

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Loop mattress suture

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A variety of suture techniques is employed by any one surgeon to achieve sound wound closure. Suture holding capacity depends not only upon the strength of the material used, the strength of the tissue into which it is inserted, the distance from the cut edges and the type of knot, but also on the suture technique employed[1]. The far–near/near–far suture to relieve skin tension, where buried sutures were undesirable, was described by Bernstein, and Burleson has described a double loop mass closure technique for abdominal wounds which actually increases wound edge apposition when a distracting force is applied[2,3].

A simple modification of the traditional mattress stitch is described. By taking the emergent thread back over the wound line to pass it through the suture loop on the opposite side before tying, a loop mattress suture is achieved (*Figure 1*). To explore the properties of this suture, a series of investigations was carried out.

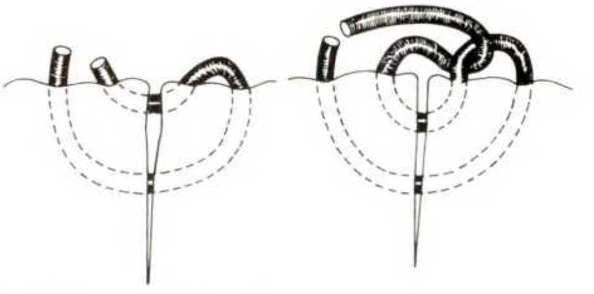

Figure 1 *The loop mattress suture*

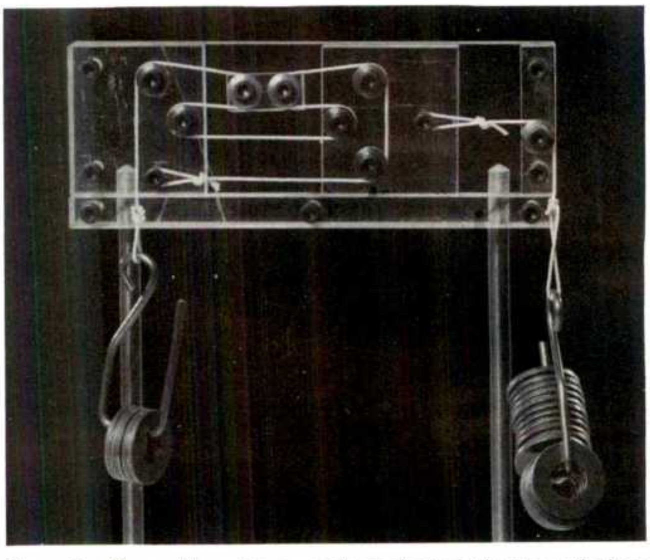

Figure 2 *The model used to gauge the mechanical advantage of a loop mattress suture*

Methods

Mechanical advantage

A model made of Perspex and brass with weights representing the wound recoil (load) and the suture pull (effort) was used to compare the mechanical advantage of the loop mattress suture, the traditional mattress suture and the plain suture (*Figure 2*).

Using an electronic force gauge, the force required using different suture techniques to achieve skin apposition in actual wounds was measured. Eighty-six sutures in thirty-two patients were studied. Skin defects were created by the excision of skin tumours and tattoos and by the raising of flaps to cover pressure sores.

It was possible to re-arrange the strands of any one suture to form, in turn, a plain stitch, a traditional mattress stitch and a loop mattress stitch, so that the only variable during such measurements was the conformation of the stitch itself. The configuration used for the first measurement varied in a random fashion, lest repeated appositions of the skin lessened the wound recoil. In each case a single throw was made and one strand fixed firmly. The force gauge was hooked onto the other strand which was slowly and steadily pulled in a horizontal direction and the suture tightened until the skin edges touched. The maximum values recorded for each suture technique were compared to assess the ease of wound apposition.

Scanning electron microscopy of recently closed wounds

A further study to examine tissue distortion and edge apposition was carried out in patients having tattoos excised. Before removal of the tattoo, a central incision was made and sutured with either loop mattress, traditional mattress or plain sutures. To prevent curling of the skin or tissue distortion during fixation, a copper splint was glued over the wound before harvesting. The excised tissue was fixed for a minimum of 48 hours in 4 per cent glutaraldehyde in phosphate buffer, then removed from the copper splint. A vertical cut was made close to a suture to display the adjacent dermis and epidermis, and the material then post-fixed in osmium tetroxide, dehydrated in ethanol and critical point dried. After sputter coating with gold, the samples were examined in a Philips 505 scanning electron microscope.

Suture performance under tension

Three leather strips were sewn together in series using a loop mattress suture at one junction and a traditional mattress suture at the other so that the edges were neatly apposed. Both sutures were subjected to the same distracting force and the occurrence of 'junction gaps' and dehiscence was recorded.

Results

Mechanical advantage

Although theoretically the suture pull (effort) should be 50 per cent of the wound recoil (load) for both the plain suture and the traditional mattress suture, using the model the figures were 65 and 75 per cent, respectively. With the traditional mattress suture, some of the work goes into skin eversion. Using the model as a loop mattress suture, the effort of wound closure was 30 per cent of the load applied.

The *in vivo* study also showed the loop mattress suture to have a genuine mechanical advantage. The average force required to achieve skin closure using the loop mattress suture (150 g) was only 62 per cent of that required using a plain suture at the same location on the same wounds (241 g). The figure for the traditional mattress suture was 106 per cent (256 g).

Scanning electron microscopy

Wounds closed with the plain suture showed some skin inversion and some dermal puckering. A small dermal gap was often noticed. The traditional mattress suture prevented skin inversion but again there was often a small dermal gap. With the loop stitch, skin apposition was good and there was minimal tissue distortion.

Suture performance under tension

Under stress the loop stitch maintained good edge apposition. When the same distracting force was applied to a traditional mattress suture a gap developed and eventually the suture either snapped or 'cheese wired' through the tissue.

Discussion

The loop mattress suture has several advantages. Firstly, because the extra loop functions as a pulley, the stitch permits the skin to be closed with less tension on the individual strands of the suture than is the case with a plain suture or the traditional mattress suture. As suture tension is reduced, less tissue damage may be expected. Furthermore, the tendency of the suture to bury itself in the skin or to 'cheese wire' through a wound during healing is diminished. Clinical use of the loop mattress suture, to close skin defects left after harvesting flaps and after excising tattoos, has been encouraging. Closure is easier and the sutures do not dig in, facilitating suture removal.

Secondly, the wound is traversed four times by the strands of the stitch rather than just twice as is the case with plain and traditional mattress sutures, thus conferring added strength to the suture.

Thirdly, skin apposition is good. The plain stitch acts as a purse string compressing and infolding the wound. Although the traditional mattress suture maintains edge eversion, the sutures may dig in and be difficult to remove. The loop mattress suture, on the other hand, distributes the force of wound closure at three levels, at the base, in the middle and at the surface of the wound. Should the wound be subject to a sudden potentially disruptive force, the traditional mattress suture will permit a small dermal gap to occur, whereas with the loop mattress suture a distracting force will tighten the central portion of the suture, maintaining dermal apposition.

In conclusion, the theoretical advantages of the loop mattress suture have been borne out in clinical practice.

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Circumumbilical versus transumbilical abdominal incision

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One hundred and fifteen patients were entered into a prospective randomized trial to establish whether midline abdominal incisions through the umbilicus produced any differences in the incidence of wound infection or failure when compared with the more conventional midline incision skirting around the umbilicus. No significant difference was shown between wound infection rates in 58 transumbilical and 51 circumumbilical incisions. Follow-up of surviving patients for at least one year showed no difference in incisional hernia rate between the two groups of patients. No problems were encountered in making the incisions through the umbilicus, but skirting the umbilicus was felt to cause problems with slewing of the scalpel blade, and asymmetry of the scar in 13 circumumbilical incisions. This study has shown that the practice of avoiding the umbilicus in midline abdominal surgery serves no useful purpose.

Keywords: Umbilicus, laparotomy, wound infection, wound healing, midline incisions

Many aspects of surgical tradition aimed at reducing the incidence of wound infection have been challenged in recent years. Orr[1] showed that the wearing of masks in theatre is not always necessary, and Hill *et al.*[2] have questioned the changing of scalpel blades after the skin incision.

We have examined the practice of circumnavigating the umbilicus when performing a midline laparotomy; this practice is anecdotal and has never been subjected to a controlled trial.

The advantages of what we have labelled the transumbilical incision are firstly speed and ease of access, and secondly an improved cosmetic result. The traditionally stated disadvantage of such an incision is an increased incidence of wound dehiscence and incisional hernia. This paper examines the evidence for this in a prospective randomized controlled trial.

Patients and methods

The trial was conducted at the East Surrey Hospital between July 1984 and May 1985. All general surgical laparotomies (elective and emergency) were randomized to be carried out through a midline transumbilical or midline circumumbilical incision. Allocation to either incision was made by a computer randomization. A sealed envelope method was used, with the envelope being opened only after skin preparation and towelling were completed. The only exceptions to randomization and inclusion in the trial were those cases in which a previous surgical incision was felt to impose on the choice of incision in this trial. No biliary or pancreatic procedure was entered into the trial since the surgeons involved preferred the use of a transverse incision for these operations.

In order to minimize the differences that might be attributable to antibiotic prophylaxis, skin preparation, surgical technique, or wound closure, a standard procedure was used in all patients. Bowel preparation used in all elective colonic surgery consisted of two doses of Picolax. Antibiotic prophylaxis was used in all contaminated or potentially contaminated operations. This consisted of a three dose regimen of metronidazole (500 mg) and gentamicin (80 mg) given intravenously.

In all cases, a non-alcoholic solution of Betadine was used for skin preparation.The umbilicus was cleaned with a Betadine soaked swab in the anaesthetic room, and in the operating theatre the abdomen was prepared with Betadine from the nipples to the symphysis pubis, then towelled in the usual manner. A sealed envelope was then opened, and the surgeon informed of the incision to be used. The transumbilical incision was made through the middle of the umbilicus. The circumumbilical incision was made by skirting to the right or the left of the umbilicus, as preferred by the surgeon. A mass closure with a continuous nylon suture was used to close the abdomen[3]. Fat layers were sprayed with povidone–iodine and the skin was closed with 3/0 nylon.

All wounds were examined daily for the presence of wound sepsis or wound dehiscence. For the purpose of this trial, a wound infection was defined as the presence of a discharge of fluid or pus from the suture line with a positive bacteriological culture.

A standard proforma was used to record the details of each case, including age, sex and antibiotic prophylaxis. The operating surgeon was invited to comment on any difficulties encountered in making or closing the incision. Development of wound complications (infection, wound dehiscence or incisional hernia) was also subsequently recorded on the same proforma sheet. In order to assess the development of incisional hernia, surviving patients were reviewed for a minimum period of one year[4].

Differences between the two groups of patients have been analysed statistically with the χ^2 test.

Results

One hundred and fifteen patients were entered into the trial over a period of 11 months. Of these, six patients were subsequently excluded. Two of these had a paramedian incision which the surgeon felt preferable after examination of the abdomen under anaesthesia. One had a perianal procedure instead of the planned transabdominal rectopexy, and in the other three cases, the incision was contained wholly above or below the umbilicus.

A total of 109 patients were included in the trial. Of these, 58 (53·2 per cent) had transumbilical incisions, and 51 (46·8 per cent) had circumumbilical incisions. The sex distribution, age and survival of patients in each group is shown in *Table 1*. In no patient was death attributable to wound complications.

Details of the operations performed through each incision are shown in *Table 2*. The numbers in each group undergoing elective *versus* emergency surgery, and clean *versus* dirty

Table 1 *Sex distribution, age and survival of patients*

	Transumbilical	Circumumbilical
Number of patients	58	51
Male:female ratio	27:31	22:29
Mean age (range)	64·2 (17–87)	65·3 (18–89)
Mean follow-up (months)	16·3	15·2
Death within 1 year	8	5

Table 2 *Operation details*

	Transumbilical ($n = 58$)	Circumumbilical ($n = 51$)
Gastric	8 (13·8%)	6 (11·8%)
Colonic cancer	26 (44·8%)	23 (45·0%)
Inflammatory bowel disease	8 (13·8%)	4 (7·8%)
Appendicitis	2 (3·5%)	3 (5·9%)
Small bowel obstruction	6 (10·3%)	4 (7·8%)
Splenectomy	1 (1·7%)	2 (3·9%)
Aortic aneurysm	2 (3·5%)	1 (2·0%)
Other	5 (8·6%)	8 (15·7%)

No biliary or pancreatic procedure was entered in the trial, because these were routinely performed through transverse incisions

Table 3 *Operative procedure: classification*

	Transumbilical	Circumumbilical
Elective	23 (39·7%)	19 (37·2%)
Emergency	35 (60·3%)	32 (62·8%)
Clean	12 (20·7%)	13 (25·5%)
Contaminated or potentially contaminated	46 (79·3%)	38 (74·5%)

operations are shown in *Table 3*. There was no significant difference between elective and emergency procedures. More patients in the transumbilical group had procedures classified as dirty (46 out of 58 patients, 79·3 per cent) but this was not significantly greater than the percentage of dirty procedures through circumumbilical incisions (38 out of 51 patients, 74·5 per cent). An acceptable stratification of patients between the two types of incision has therefore resulted from the randomization procedure.

Wound infections

A total of 17 patients developed wound infections. These occurred in 9 out of 58 patients (15·5 per cent) having transumbilical incisions, and 8 out of 51 patients (15·7 per cent) with circumumbilical incisions. Details of operations and bacteriological studies of these infections are shown in *Table 4a* and *b*. Over 50 per cent of wound infections were caused by coliform organisms. No patient with a transumbilical incision developed sepsis in relation to the umbilical part of the wound, but one patient in the circumumbilical group (elective right hemicolectomy) developed infection in the wound adjacent to the umbilicus. In neither group were there any infections in the operations classified as clean.

Statistical analysis showed no significant difference between the wound infection rates of the two types of incision ($\chi^2 = 0·0083$; $P > 0·5$).

Incisional hernia and wound dehiscence

Three of the 109 patients included in the trial developed incisional hernias. Of these, one patient (small bowel resection for adhesive obstruction) had a transumbilical incision, and two patients (repair of ruptured aortic aneurysm and right hemicolectomy) had circumumbilical incisions. All incisional hernias occurred in patients having emergency operations. Two of them also had wound infections. No significant difference was demonstrated between the two groups ($P > 0·1$). There were no wound dehiscences.

Surgeon's comments

The operating surgeon was invited to comment on any problems encountered while making or closing an incision. No surgeon commented on difficulty in making a transumbilical skin incision, but 13 incisions in the circumumbilical group were considered troublesome. In every case, the opinion expressed was that the scalpel blade tended to slew obliquely through the skin, and that it was difficult to produce a symmetrical curve around the umbilicus. Closure of the skin was found to be difficult in six patients with transumbilical incisions. These patients were obese (mean weight 89·2 kg) and the problem encountered was in placing sutures within a deep umbilicus. Additionally, in four out of these six patients, difficulty was reported in removing sutures from within the umbilicus.

Discussion

Whilst careful avoidance of the umbilicus has become the rule with midline laparotomies, no trial has been undertaken to establish the necessity of this practice. Indeed, skirting the umbilicus has become so ingrained into surgical practice that leading surgical texts[5,6] and reviews on abdominal incisions[7,8] advocated it without mention of even the theoretical disadvantages of taking the incision through the umbilicus.

The reasons for avoiding the transumbilical incision are obscure but clearly the concept of the umbilicus as a source of wound infection must have led to the use of the circumumbilical incision. Additionally, as the umbilicus is a scar, a greater wound failure rate could be envisaged with the transumbilical incision.

The results of this trial have shown that the avoidance of the umbilicus offers no benefit with regard to wound infection, dehiscence, or incisional hernia rate when compared to the transumbilical incision. Both contaminated and clean procedures have been included in the trial. All contaminated procedures received prophylactic antibiotics and since the percentage of such procedures in each group is similar (79·3 per cent transumbilical; 74·5 per cent circumumbilical), any difference in wound sepsis rates that might be attributable to prophylactic antibiotics is not significant.

No surgeon in this trial found any difficulty in entering the abdomen through a transumbilical wound. Whilst difficulty was encountered in placing and removing sutures within the umbilicus in six obese patients, we have since found the wounds heal readily without the need for skin sutures in the base of the umbilicus.

Table 4a *Details of transumbilical wound infections*

Age	Sex	Operation	Organism
67	M	Hartmann's for colovesical fistula	*Klebsiella* sp.
78	M	Ileotransverse anastomosis for carcinoma of colon	*Escherichia coli*
49	M	Perforated jejunal diverticulum	*E. coli* *Pseudomonas* sp.
76	F	Strangulated fem. hernia, small bowel resection	*E. coli*
44	M	Right hemicolectomy	*Streptococcus pneumoniae* *E. coli*
60	M	Anterior resection	*E. coli*
49	M	Polya gastrectomy	*S. faecalis*
73	M	Right hemicolectomy	*Pseudomonas* sp.
82	M	Diverticular abscess	*E. coli*

Table 4b *Details of circumumbilical wound infections*

Age	Sex	Operation	Organism
59	M	Diverticular abscess	Mixed coliforms
63	M	Anterior resection	*E. coli*
55	M	Right hemicolectomy	*Bacteroides* sp. *Klebsiella* sp.
46	M	Colovesical fistula	*Staphylococcus aureus* *E. coli*
69	F	Oversew perforated duodenal ulcer	*S. aureus*
72	M	Small bowel obstruction	*E. coli*
80	M	Appendicectomy	*Bacteroides* sp.
79	F	Gallstone ileus	*Proteus* sp.

Many surgical rituals have been challenged in recent years. This study has shown that the circumumbilical incision is a surgical myth and should be replaced by the more symmetrical and more logical transumbilical incision.

Acknowledgements

We are most grateful to the consultant surgeons at the East Surrey Hospital, Mr I. D. Hunter-Craig, Mr R. G. Lightwood, Mr J. E. Hale and Mr M. C. Jennings, for their encouragement and co-operation. We would also like to acknowledge the help of the surgical house officers and theatre staff who were involved in this trial.

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Case report

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'Button hole' incisional hernia: a late complication of abdominal wound closure with continuous non-absorbable sutures

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Mass closure of midline abdominal incisions with a continuous non-absorbable suture is popular because of the low incidence of wound dehiscence[1-3] but late wound failure, manifest as incisional herniation, remains problematic[1,2,4-6]. The majority of incisional hernias develop in the first year and are the result of the interaction of a number of factors including the method of closure, the suture material used, wound infection and age and sex of the patient[1,2,6,7]. There is, however, an incidence of late presentation which is difficult to explain on a mechanical basis[4,5]. Two patients with multiple small wound hernias presenting several years after operation are described, and a hypothesis proposed to explain the late development of some hernias in patients whose wounds are closed with continuous non-absorbable sutures.

Case report

Case 1

In October 1979 a 67-year-old man underwent elective cholecystectomy through an epigastric midline incision. The wound was closed with a mass technique using continuous 4 metric polypropylene. There were no postoperative problems and, in particular, no evidence of wound infection. He was discharged from follow-up after 6 months and presented again in June 1982 with multiple small asymptomatic epigastric hernias. Four years later the hernias were larger and symptomatic (*Figure 1*). At operation in May 1986 the linea alba was intact but there were several bilateral oval 'button hole' defects through which preperitoneal fat protruded. These lateral protrusions were at the sites of penetration of the rectus sheaths by the continuous polypropylene suture. The defects varied in size from 1 to 3 cm and were individually repaired with 2 metric polydioxanone after removal of the polypropylene suture. Recovery was uncomplicated and the repair remains intact to date.

Case 2

In May 1976 a 48-year-old fisherman underwent elective vagotomy and pyloroplasty. An epigastric midline incision with mass closure with continuous 4 metric polypropylene was used. The wound healed primarily. In April 1985 he presented with multiple symptomatic epigastric hernias which had increased in size over the previous 5 years. At operation a similar number and distribution of lateral defects in the rectus sheaths (*Figure 2*) were found and individually repaired with 2 metric polypropylene. Recovery was straightforward and the repair remains intact to date.

Discussion

An incisional hernia develops in approximately 10 per cent of patients in whom a midline incision is closed with a continuous mass non-absorbable suture[1,2,6,7]. The majority present in the first year and are related to age, sex, obesity, chest infection and wound sepsis[1,2,6,7]. These 'early' hernias are attributable to mechanical wound failure. The combined strength of the healing wound, a function of the 'extrinsic' strength, dependent on the

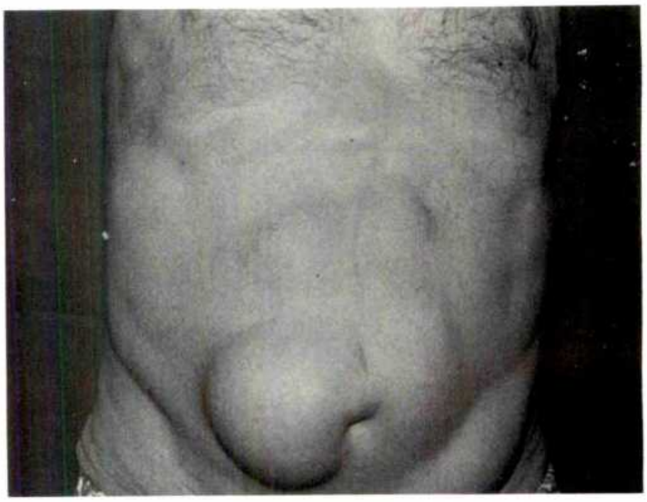

Figure 1 *Multiple eccentric hernias apparent in relation to previous midline epigastric incision (case 1)*

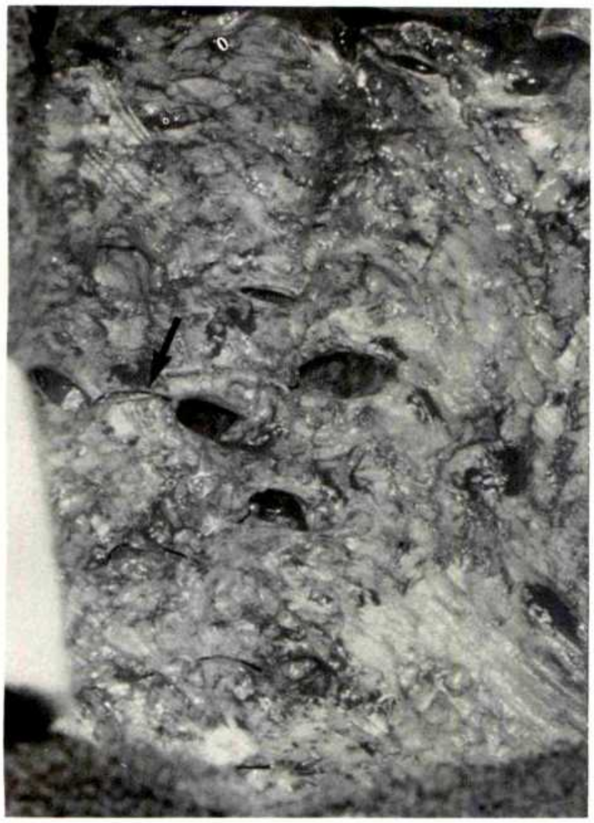

Figure 2 *Operative appearance of multiple 'button hole' hernias with the continuous polypropylene suture (arrowed) connecting the medial edges of the paired defects (case 2)*

mechanical aspects of wound closure, and the slowly increasing 'intrinsic' strength is inadequate to withstand the forces applied and a diffuse hernia results. It is logical to expect an increased incidence of 'early' incisional hernia when absorbable suture material with a relatively short retention of strength is used[2].

The development of hernias long after the wound has matured is more difficult to explain. Hernias which present after the first year are often small and sharp edged[4,8] and their aetiology is obscure. The concepts that mature collagen should stretch to result in herniation more than a year after operation or that small tight hernias are the result of localized deep-seated infection[8] were not acceptable to Ellis and his colleagues[4]. We believe that some late hernias are the result of persistence of continuous suture material with the hernias developing at the sites of penetration of the abdominal wall. The effect of slight but repeated movement of the suture in relation to the abdominal wall over the years may be akin to the sawing effect of a cheese wire as suggested by the appearances in *Figure 2*. Whether an interrupted technique would result in a similar effect is uncertain.

An optimal suture length to wound length ratio of at least 4:1 is important in the avoidance of dehiscence[3] and may also be a factor in the prevention of 'button hole' hernias. Although the ratio was not measured in these two patients operated on in 1976 and 1979, the ratio was prospectively recorded in 283 consecutive patients during 1977–1978 using a similar technique. The median ratio was 4·3:1 and it is probable that an adequate length of suture was used in both these patients.

Late hernias also occur when absorbable sutures are used[4] and the advantage of non-absorbable over most absorbable materials has been a lower overall incidence of incisional hernia[1,2,6,8]. The persistence of non-absorbable suture material has not previously been thought to be detrimental except in relation to wound pain and sinus formation. The appearance of 'button hole' hernias associated with the persistence of a non-absorbable continuous suture long after its function has been served supports our recent opinion that polydioxanone is a preferable suture material to polypropylene for continuous mass closure of midline wounds[7].

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826

The stabilized ring retractor: a technique for cholecystectomy

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Holding a liver retractor during a long and difficult cholecystectomy is an unhappy memory for many students and house surgeons. Maintaining the retractor steady and in a good position is difficult because the assistant cannot see its tip. Similar difficulties are encountered during vagotomy, and for this the Goligher retractor is commonly used[1]. Recently, the Omnitract retractor (CLS Medical Ltd, Sheffield, UK) has been found to be useful during aortic surgery[2]; here, a similar retractor is described for use in cholecystectomy.

Method

An 8 cm transverse incision is made in the right upper quadrant, cutting the rectus sheath and muscle transversely without extending beyond the borders of the rectus sheath. The retractor is then placed over the towels and attached to the side rail of the table (*Figure 1*). A Kelly retractor is then attached to the ring lifting up the under surface of the liver to expose Calot's triangle. A pack is inserted over the hepatic flexure and duodenum, and retracted downwards by a malleable blade which is also attached to the ring. The head of the table is raised 30° to improve exposure. A clamp is placed on the gallbladder and then the cystic duct and cystic artery are dissected with the aid of Turner-Warwick's diathermy scissors. A peroperative cholangiogram is obtained through a cannula held in place by a ligaclip[3]. The cystic artery, after clear dissection, is divided between ligaclips. A fundus first cholecystectomy is performed using the diathermy scissors to obtain meticulous haemostasis. The peroperative cholegram is inspected to assess anatomical landmarks, and the duct is ligated between ligaclips so enabling removal of the gallbladder. At no stage is a hand inserted in the abdomen and dissection is performed entirely with instruments. The abdomen is closed with interrupted No. 1 polydioxanone by the mass closure technique and the skin sutured with a subcuticular 3/0 polydioxanone suture. Suction drainage is provided to the subhepatic space on some occasions. The patient is started on free fluids on the first postoperative day and aggressive mobilization advised.

Discussion

This technique gives good exposure of the anatomy of the porta hepatis without the constant movement of the hand held retractor, enabling accurate dissection of important landmarks. The first assistant is freed from retractor holding, and can be dispensed with by the experienced operator. The important advantage of this retractor is that it can be applied to the operating table over the towels, it can be removed during the peroperative cholangiogram with easy re-application and the tilt of the ring and of the retractors can be varied easily. The avoidance of a full laparotomy ensures that there is no contamination of the abdominal cavity and postoperative ileus is limited. In the last 35 cholecystectomies using the technique, the mean postoperative hospital stay has been 4·4 days with nine patients having clinically evident atelectasis and three patients having a minor wound infection. We commend this technique to the experienced biliary surgeon.

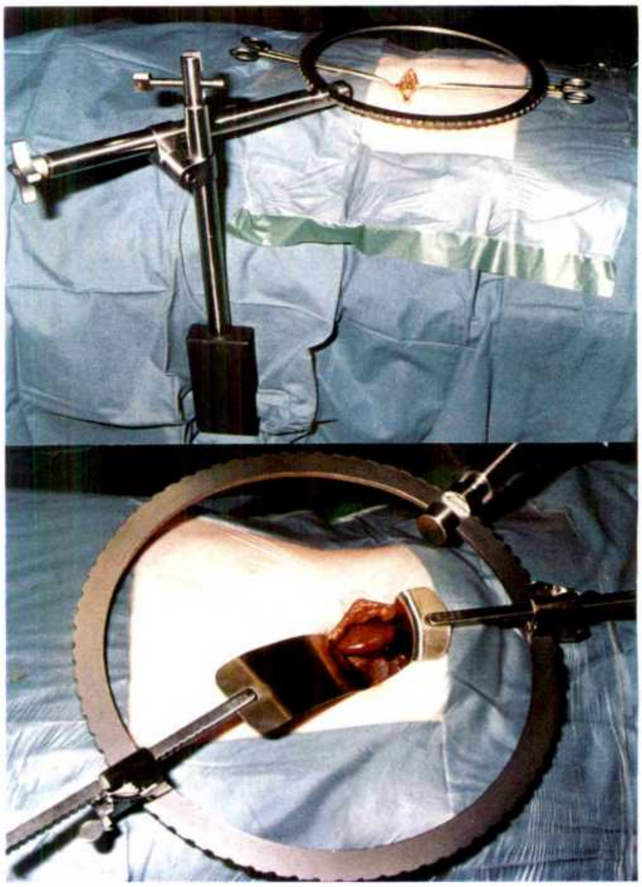

Figure 1 *The Bookwalter retractor*

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The Bookwalter retractor is marketed by Codman and Shurtleff Inc., New Bedford, Massachusetts 02746, USA

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Out-patient treatment of haemorrhoids with bipolar diathermy coagulation

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Haemorrhoids are a common complaint with distressing local symptoms from which the patient seeks relief. A variety of out-patient techniques are described for symptomatic first and second degree haemorrhoids which include sclerotherapy[1], rubber band ligation[2], and photocoagulation[3], which will often result in symptomatic relief without recourse to formal haemorrhoidectomy. We describe a new technique using contact bipolar diathermy and report results.

Patients and methods

Forty-three patients with symptomatic first and second degree haemorrhoids were treated by contact bipolar diathermy in the out-patient clinic. Seven patients had had previous treatment by sclerotherapy within 5 years of presentation.

The patient was placed in the left lateral position and a plastic disposable proctoscope inserted into the anorectum. The diathermy probe (*Figure 1*) was laid directly onto the base of the haemorrhoid ensuring that the tip was well above the dentate line. The BICAP bipolar diathermy generator (750 kHz, 50 W) controlled by a foot switch was used to coagulate the haemorrhoid (approximately 10 s). Each patient was reviewed monthly.

Further studies were carried out on two resected rectums to assess the depth of coagulation and local temperature changes. Thermocouples were placed at varying depths from the epithelial surface and bipolar diathermy applied as for treatment of haemorrhoids. Temperature changes were recorded and the depth of thermal injury assessed by histological examination of the tissue.

Results

All patients were treated as out-patients with no patient requiring admission to hospital after treatment.

Twenty-six patients experience relief of presenting symptoms after one treatment (*Table 1*). Fourteen patients (33 per cent) gained symptomatic relief with two treatments. Two patients required three treatments with the remaining patient requiring formal haemorrhoidectomy after failure of bipolar diathermy to control his symptoms. Eighteen patients (41 per cent) experienced mild to moderate discomfort during the procedure which persisted in seven for more than 48 h.

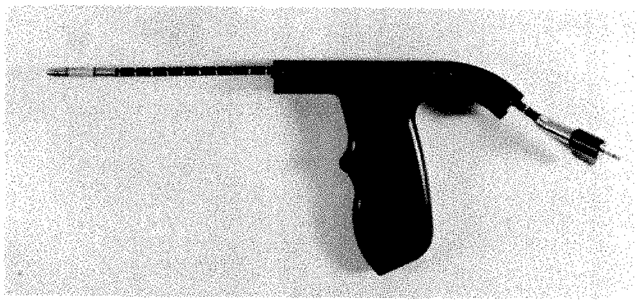

Figure 1 *The prototype bipolar diathermy probe with handle*

Table 1 *Number of patients experiencing symptoms before and after treatment*

	At presentation	After initial treatment
Bleeding	40	11
Prolapse	10	2
Discharge	8	3
Anal discomfort	0	7

The temperature rise, during bipolar coagulation was recorded at 25°C 1 mm deep to the mucosa falling to 0°C at a depth of 6 mm. This temperature rise was experienced by 10 of the 43 patients as a mild sensation of local heat during treatment of the haemorrhoids.

Histological sections of the coagulated tissue showed a typical diathermy effect with 'streaming' of the nuclei in the epithelium and the sub-epithelial layer. The immediate depth of thermal injury was 3 mm.

Discussion

The destruction of haemorrhoidal tissue by the application of local heat to cause coagulation was probably first described by Cusack in 1846[4] in his account of the clamp and cautery method of operative haemorrhoidectomy, a technique noted for the lack of postoperative pain and freedom from anal stenosis. Bipolar diathermy coagulation of haemorrhoids was well tolerated by our patients with relief of symptoms of rectal bleeding and prolapse within one to three treatments. Contact bipolar diathermy was not associated with significant anal discharge as is often seen following cryotherapy.

Photocoagulation of haemorrhoids requires an average of three treatments for each haemorrhoid because the area of coagulation per treatment is small (3 mm), reference 5. The depth of coagulation is similar to infra-red photocoagulation and bipolar diathermy (3 mm) but the length of the coagulum is approximately 1 cm which may reduce the number of treatments required to achieve relief of symptoms. Bipolar diathermy carried out at the time of the initial proctoscopic examination of the patient is quick, easy to administer and relatively painless. This technique does not require an assistant to steady the proctoscope, unlike many rubber band applicators. Results are comparable with established out-patient methods of treatment and bipolar diathermy coagulation of haemorrhoids should be considered as a viable alternative treatment.

Acknowledgement

We are most grateful to American ACMI for the loan of the BICAP generator and haemorrhoid gun.

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Polydioxanone or polypropylene for closure of midline abdominal incisions: a prospective comparative clinical trial

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Seven hundred and fifty-seven consecutive patients undergoing a midline abdominal incision were stratified according to age, sex, type of operation and degree of operative contamination and were randomly allocated to mass closure of the abdominal wall with continuous 4 metric polydioxanone (PDX; 374 patients) or continuous 4 metric polypropylene (PPL; 383 patients). Wound infection was less common with PDX (PDX 3·5 per cent; PPL 7·0 per cent; $P<0{\cdot}05$*) and there was one dehiscence in each group. The incidence of defective wounds in patients surviving 1 year was similar (7·7 per cent PDX; 9·7 per cent PPL) but the PPL suture had to be removed because of persisting wound pain or sinus formation in five patients. PDX is the preferred suture material for closure of midline abdominal incisions.*

Keywords: Midline incision, incisional hernia, polydioxanone, polypropylene

The vertical midline incision is popular for abdominal surgery because of its simplicity, versatility and ease of closure when a continuous mass suture technique is used. Tension-free closure with large tissue bites reduces the frequency of wound dehiscence and evisceration to very low levels[1] but there is an incidence of late wound failure manifest as incisional herniae. Wound failure is a function of the extrinsic strength of the wound, dependent on the material and technique used for closure[2] and the rate of recovery of intrinsic strength in the healing wound. The relatively rapid loss of tensile strength in both natural and synthetic absorbable suture materials has led to the use of synthetic nonabsorbable materials, in particular monofilament polypropylene (PPL) or polyamide, for closure of midline incisions.

Polydioxanone (PDX) is a synthetic monofilament absorbable suture material with a higher breaking strength than monofilament PPL or polyamide. It is relatively inert in tissues and retains its strength for longer (40 per cent at 6 weeks) than other absorbable materials. Early experience with PDX for closure of midline wounds has been favourable in terms of early wound failure[3,4] but in a small study[5] a high incidence of incisional herniation at 1 year led to a recommendation that PDX was unsuitable for mass closure of midline wounds.

We report the results of a large prospective trial comparing PDX and PPL in this situation.

Patients and methods

All patients undergoing laparotomy through a vertical midline incision under the care of two consultants (J.E. and N.A.M.) were stratified according to age (above or below 60 years), sex, type of operation (whether emergency or elective) and the degree of operative contamination (clean, clean/contaminated, contaminated or dirty[6]) before allocation to closure with either 4 metric PDX or 4 metric PPL according to computer-generated randomization tables. Patients undergoing repair of incisional herniae were the only exclusions.

The overall operative, antibiotic and management policies were as previously described by us[7].

The abdominal wall was sutured with a tension-free continuous mass closure technique using a 50 mm reverse cutting needle taking tissue bites of at least 1 cm not more than 1 cm apart. Knots which were always buried deep to the linea alba were tied either by hand or with an instrument, depending on the operator's preference. Skin closure was with interrupted monofilament polyamide mattress sutures removed on the tenth postoperative day.

Wound infection was defined as the discharge of pus from the wound or the growth of a pathogenic organism from a serous or sanguinous discharge. All patients were reviewed at 4–6 weeks after discharge from hospital and any reported discharge from the wound was recorded as a wound infection. Dehiscence was recorded when evisceration occurred.

Direct enquiry was made as to the persistence of wound pain or suture awareness at follow-up at 4 weeks and 12 months. Any reported pain was recorded as moderate or, if analgesics were taken by the patient, graded as severe.

Wound strength was assessed at each follow-up by observing and palpating the abdominal wall while the patient lay supine and flexed the extended legs at the hips. Wound failure was recorded if there was a palpable gap without obvious herniation, a diffuse bulge or obvious herniation. At the time of assessing wound integrity the observer was unaware of the suture material used. In 21 patients unable to attend the information was obtained from the general practitioner.

Additional information on diagnoses, operative procedure, postoperative complications and antibiotic therapy was recorded prospectively.

The data were stored and analysed using the Statistical Package for Social Scientists on a Honeywell 66/80 mainframe computer. The χ^2 test with Yates' correction was used for all statistical comparisons.

Results

A total of 757 patients were entered into the trial, 374 in the polydioxanone group (PDX) and 383 in the polypropylene group (PPL). The two groups were well matched according to age, sex, type of operation and degree of operative contamination (*Table 1*).

Wound infection developed in 13 (3·5 per cent) of the PDX group and 27 (7·0 per cent) of the PPL group; the difference was significant ($P<0{\cdot}05$) (*Table 2*). There was one wound dehiscence in each group giving an overall incidence of 0·26 per cent.

Of the original 757 patients 38 (5·0 per cent) died before follow-up at 4 weeks; 14 patients were lost to follow-up and 705 (98·1 per cent) of the survivors were reviewed 4 weeks after discharge from hospital. An additional 95 patients were known to have died within 12 months and 30 patients were lost to follow-up. Five hundred and eighty (95·1 per cent) of the survivors were reviewed at 12 months.

At 4 weeks wound pain was present in 48 (14·0 per cent) of PDX patients and 53 (14·6 per cent) of PPL patients and was severe in 9 (2·6 per cent) and 10 (2·8 per cent) respectively. At 12 months nine (3·2 per cent) PDX patients had pain which was

Table 1 *Comparability of the study groups*

	PDX	PPL
Sex		
Male	193	206
Female	181	177
Age		
Under 60 years	182	188
Over 60 years	192	195
Type of operation		
Emergency	124	124
Elective	250	259
Operative contamination		
Clean	92	102
Clean/contaminated	194	190
Contaminated	27	31
Dirty	61	60
Overall	374	383

PDX, polydioxanone; PPL, polypropylene

Table 2 *Relationship of operative contamination and wound infection (WI) in 757 patients*

Degree of contamination	PDX			PPL				
	No.	WI	%	No.	WI	%	χ^2	P
Clean	92	2	2·2	102	8	7·8	2·13	>0·1
Clean/contaminated	194	4	2·1	190	7	3·7	0·42	>0·1
Contaminated	27	1	3·7	31	3	9·7	0·14	>0·1
Dirty	61	6	9·8	60	9	15·0	0·34	>0·1
Overall	374	13	3·5	383	27	7·0	4·14	<0·05

PDX, polydioxanone; PPL, polypropylene

Table 3 *Age, sex, type of operation and late wound failure in 580 patients reviewed at 1 year*

	No.	Wound failure	%	χ^2	P
Age					
Less than 60 years	325	19	5·8		
Over 60 years	255	31	12·2	6·68	<0·01
Sex					
Female	278	9	3·2		
Male	302	41	13·6	18·35	<0·001
Type of operation					
Elective	423	39	9·2		
Emergency	157	11	7·0	0·44	>0·5

Table 4 *Influence of wound infection on late wound failure in 580 patients reviewed at 1 year*

	No.	Wound failure	%	χ^2	P
Polydioxanone					
Uninfected	276	21	7·6		
Infected	9	1	11·1	0·06	>0·5
Total	285	22	7·7		
Polypropylene					
Uninfected	273	20	7·3		
Infected	22	8	36·4	16·75	<0·001
Total	295	28	9·5		
Overall					
Uninfected	549	41	7·5		
Infected	31	9	29·0	14·69	<0·001
Total	580	50	8·6		

severe in only one (0·4 per cent). In contrast 18 (6·1 per cent) PPL patients had pain which was severe in 7 (2·4 per cent). These differences were not significant. The PPL suture was removed in four (1·4 per cent) patients because of pain and one patient (0·3 per cent) developed a persistent wound sinus necessitating removal of the nonabsorbable suture. This was the only wound sinus in the series.

At 4 weeks 3 (0·9 per cent) of 343 PDX patients were considered to have a defective wound with frank herniation in 1 (0·3 per cent). There were 7 (1·9 per cent) defective wounds in 362 PPL patients with frank herniation in 3 (0·8 per cent). At 12 months there were 22 (7·7 per cent) defective wounds in 285 PDX patients including 10 (3·5 per cent) with frank herniae. There were 28 (9·5 per cent) defective wounds in 295 PPL patients including 14 (4·7 per cent) frank herniae. These differences were not significant.

The relationship of age, sex and type of operation to the strength of the wound at 1 year is shown in *Table 3*. The incidence of late wound failure was significantly greater in patients aged over 60 years and in men but was not related to the type of operation. There was no significant difference in the total incidence of late wound failure comparing PDX (7·7 per cent) with PPL (9·5 per cent). The incidence of late failure was four times as high after wound infection compared with non-infected wounds and this difference was significant ($P < 0·001$) (*Table 4*). The higher overall incidence of wound infection with PPL (*Table 2*) was associated with a threefold increase in incidence of late wound failure (PPL 36·4 per cent) compared with PDX (11·1 per cent) when wound infection developed but this difference was not statistically significant (*Table 4*).

There was no difference when knots were tied by hand or with an instrument.

Discussion

Continuous mass closure with either monofilament nonabsorbable sutures[8,9], wire[8] or braided synthetic absorbable sutures[8,9] is an effective method for reducing postoperative wound dehiscence but the absorbable materials have been associated with an unacceptably high late failure rate in terms of incisional herniation[8,9]. The increased incidence of herniae is attributed to the relatively rapid loss of tensile strength in the absorbable material such that the extrinsic strength of the healing wound is insufficient to resist the forces applied to it. There is, however, no reduction in the tensile strength of nonabsorbable materials although a degree of elongation occurs with synthetic polymers. Monofilament materials have less than ideal knotting characteristics and may break if the surface is traumatized. There is a significant incidence of wound pain and suture awareness with nonabsorbable materials and wound infection with sinus formation is more common than with absorbable materials[8–10].

PDX is a synthetic absorbable material which when supplied as a monofilament of similar diameter has a tensile strength 1·7 times greater than PPL[4] and which retains approximately 50 per cent of its strength for 5 weeks. Early experience with PDX for mass closure has been favourable[3,4] although a pilot study comparing PDX with polyamide suggested an unacceptably high incisional hernia rate[5]. This is the first large prospective trial to be reported comparing the two materials including assessment of the frequency of incisional herniation at 1 year.

Old age, male sex and wound infection[8,11] are important determinants of early wound failure and in this study were significant factors in late failure (*Tables 3* and *4*). There was, however, no significant difference between the two suture materials in terms of either dehiscence, one in each group, or incisional herniae at 1 year. Wound infection (*Table 2*) was significantly more common when the nonabsorbable material was used (7·0 per cent PPL; 3·5 per cent PDX). The infection rates were higher for all degrees of operative contamination for PPL compared with PDX although the differences were not significant. The higher overall incidence of wound infection with PPL was associated with a threefold increase in the incidence of late wound failure compared with PDX when wound infection developed though the difference was not statistically significant. The two groups were comparable in terms of operative contamination and a consistent antibiotic policy was followed suggesting that the suture material was itself influential in the genesis of postoperative sepsis. It is not clear why there should be such a difference when the physical characteristics of the two materials in the first 3 weeks are essentially similar.

The incidence of wound failure at 1 year may not reflect the ultimate outcome in so far as incisional herniae continue to present after this time[12,13]. The aetiology of herniae presenting in the early postoperative period may be different from those presenting late. A large proportion of these late herniae are small, well-defined defects[12] and the persistence of the nonabsorbable suture may be detrimental in some patients producing a series of 'button hole' type defects remote from the incision.[14].

The overall wound infection rate, including late infections, was relatively low (5·3 per cent) but not as low as we have previously reported when the number of operators was much smaller and the details of patient management and operative practice more closely controlled[15]. Nevertheless the overall rates of incisional herniae and virtual abolition of wound sinus formation (1 case in 757 operations) are probably attributable to the infrequency of septic complications, the variable most amenable to modification by surgical practice[8].

If a continuous suture is used for closure the optimum ratio of suture length to wound length is approximately 4:1[1]. This ratio was not measured during the trial but in a previous 283 patients in whom the same technique was used and the ratio measured the median was 4·5:1 (range 2·9–8·3).

Although the overall incidence of wound failure was 8·6 per cent (50 out of 580 patients) only 24 of these patients had a definite hernia, the remainder having a palpable gap with no protrusion or a diffuse asymptomatic bulge. This figure is higher than can be achieved with the lateral paramedian incision[16,17] but in our opinion the advantages of the midline incision compensate for this deficiency. Severe wound pain persisted in 2·4 per cent of patients when PPL was used and the nonabsorbable suture had to be removed in five PPL patients.

Despite previously expressed doubts as to the suitability of PDX[5] for midline closure we have shown no disadvantage in terms of wound failure compared with the nonabsorbable PPL and definite advantages in terms of decreased wound infection and avoidance of the need for suture removal. In conclusion, PDX is a preferable material to PPL for midline wound closure.

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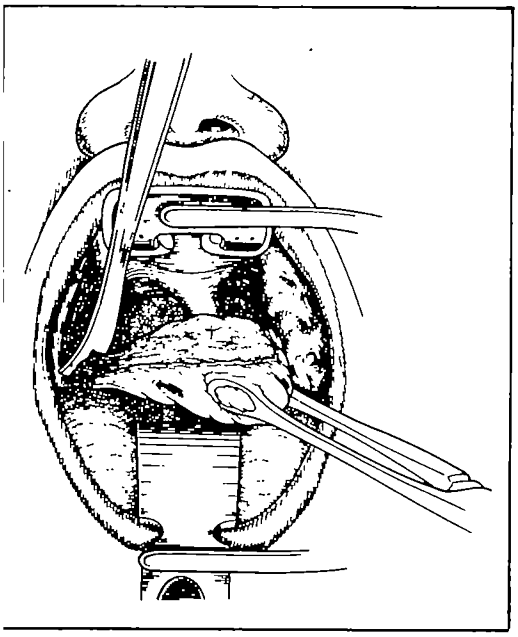

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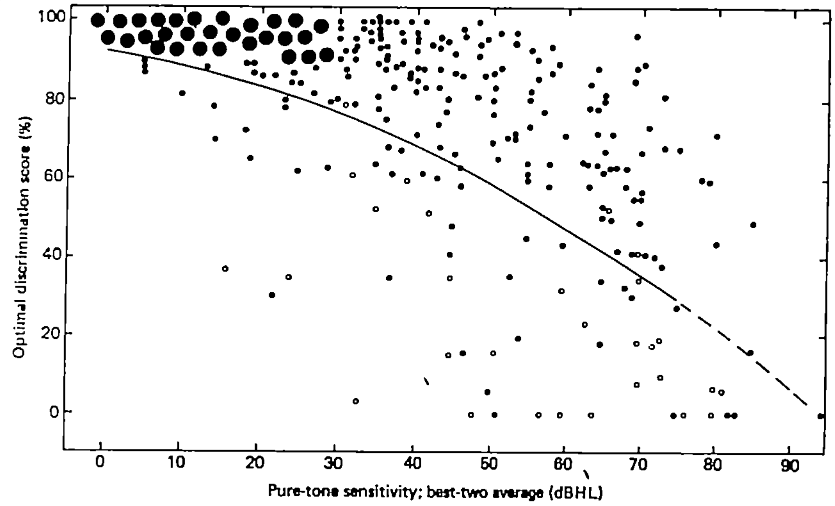

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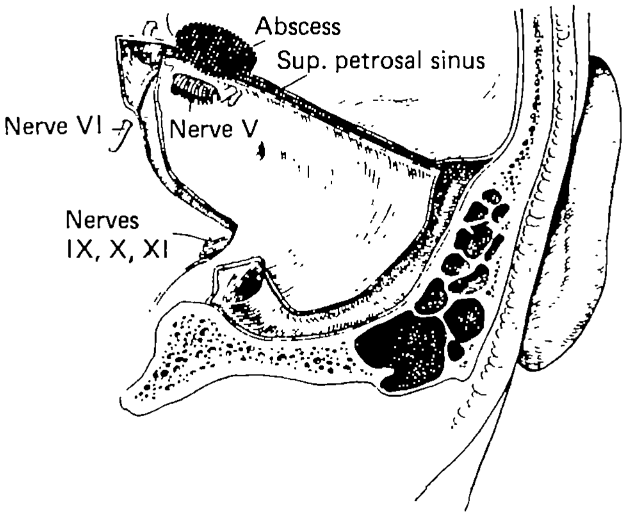

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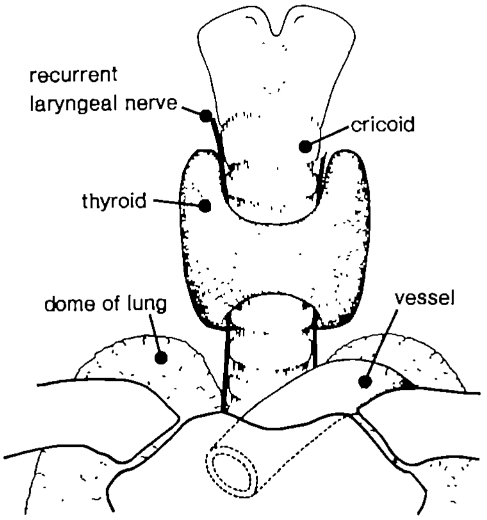

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Assessment of hospital workload in war surgery

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The aim of treatment of casualties in war time is to offer a chance of survival to the greatest number of patients. This goal can be approached by selecting for treatment patients who have a real chance of survival and by reducing the duration of operations as much as possible. Should the operative time be limited to an assessed predetermined duration as proposed in certain armies? Conditions for the observation of war wounded were particularly favourable in the ICRC (International Committee of the Red Cross) Hospital in Peshawar (Pakistan) because all treatments were started and completed in the same place. During the summer of 1985, a major battle took place near the Pakistan border. Analysis of 212 operated patients, of whom 68 per cent arrived at the hospital less than 48 h after the injury, showed that the operations lasted 90 min on average. Abdominal procedures were the longest. Patients stayed in the hospital for an average of 4 weeks; those with lesions of the extremities stayed longer (5·8 weeks) than those with abdominal or thoracic lesions (4·3 and 3 weeks). The results show that the long duration of an operation has not been correlated either with an unfavourable outcome or with an increased postoperative workload. As far as possible, accelerating the turnover of operations by increasing the number of operating teams should be the objective rather than the selection of patients who require short operations. Such selection would have resulted in the death of most seriously wounded patients in this series.

Keywords: War surgery, operative time, prognosis

Operative strategies in war surgery are directed to offer a chance of survival to the greatest number of wounded. Discrepancy between need and resources impose the requirement for triage, where only patients who have a real chance of survival will be treated, using as far as possible simple procedures. This last requirement has been laid down in principle in some armies, whose planning has included an average operative time[1]. Reports concerning this particular point are however rare in the medical literature.

During recent wars, improvements in evacuation procedures have made possible the transfer of patients to distant hospitals at different stages of treatment; the overall evaluation of treatment has thus become more difficult.

The particular situation of the International Committee of the Red Cross (ICRC) Hospital in Peshawar, Pakistan, and its activities during the summer of 1985 made it particularly suitable for an overall evaluation of the time spent operating upon different types of wounds and allowed a complete observation of outcome after treatment.

Patients and methods

Situation, circumstances and conditions of work

The ICRC Hospital in Peshawar is devoted to the treatment of wounded victims of the Afghan war. It is situated 40 km from the border of Afghanistan and has a capacity of 130 beds. Two surgical teams each composed of one surgeon and one Afghan doctor, two anaesthetist nurses and two operating nurses, work in two different operating theatres[2]. Instruments are simple and purchased in Pakistan with the exception of the external fixators for fractures which are imported from Switzerland (AO system)[3].

A variety of anaesthetic methods is available: local, regional or general using ketamine or halothane (Fluothane) with endotracheal intubation. Blood transfusions are organized by the hospital laboratory, and blood is provided by patients' relatives. Ringer lactate, saline and glucose solutions as well as antibiotics are available from the pharmacy.

During the summer of 1985, a major battle took place in the Afghan province of Paktia, bordering Pakistan, involving approximately 18 000–20 000 men. Although the usual strategy of the Afghan resistance has been to wage a guerilla war, a more conventional battle took place at that time. This resulted in an increased activity in the ICRC hospital whose occupation rate doubled within 2 weeks. Towards the end of the battle, which lasted about 3 weeks, an extra surgical team was flown in and then a field hospital with an operating theatre and room for over 100 patients was provided by the ICRC to relieve the main hospital which had been overloaded for 3 weeks.

Management

The data presented here are those collected by the Swiss team working in the ICRC hospital over a period of 3 months, concerning 212 patients treated entirely by this particular team. (During this period of time 712 patients were treated by the different teams working in the hospital.)

Most of the patients were male, aged between 16 and 60 (83 per cent). Children (12 per cent) and women (5 per cent) were a minority. Nearly all the wounds were caused by missiles among which shelling injuries were the most frequent. Burn injuries were rare. Fifty-five per cent of patients were treated within 24 h after injury; however, delays for some were much longer (*Figure 1*).

Wounds of varying severity were observed and assessed; 30 per cent of patients had multiple injuries. *Figure 2* shows the distribution of lesions. Most of the patients had injury to the extremities. Trauma to the head, thorax and abdomen were less frequent. Lesions to the extremities were treated by debridement and delayed wound closure, usually performed 10 days later; fractures were stabilized in 18 cases with external fixation (11 lower and 7 upper limbs).

Traction was used in 4 cases for comminuted fracture of the proximal femur and in 10 cases for simple fracture of the leg with subsequent casting. Twenty-six amputations of the lower and three of the upper limbs were performed. These procedures were initially refused by some of the wounded and had to be performed later under less favourable conditions. Thoracic wounds were treated in 16 cases by simple chest tube drainage. Thoracic intervention was necessary in five cases (two thoracic wall defects, one perforation of the diaphragm with stercoral peritonitis and pleuritis, one oesophageal perforation, one chronic pyopneumothorax). Abdominal trauma was associated with a thoracic lesion in six cases.

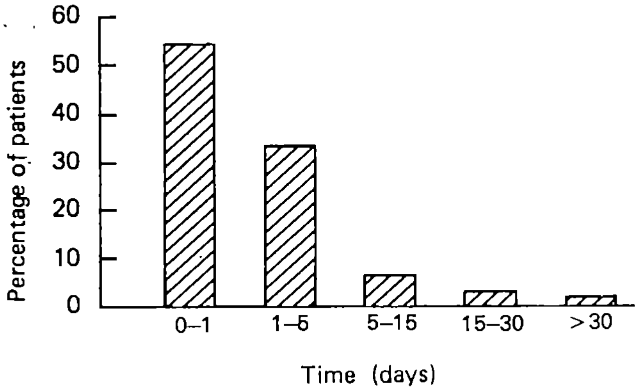

Figure 1 *Delay between injury and hospital treatment was less than 1 day in 55 per cent of cases. In 11 per cent of cases, it was greater than 5 days*

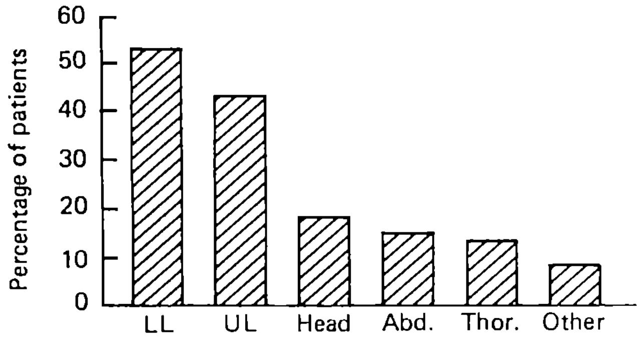

Figure 2 *Distribution of injuries (LL, lower limbs; UL, upper limbs; Abd., lesions of the abdomen; Thor., lesions of the thorax; Other, lesions of the perineum or of the back with involvement of the spine). Lesions of the extremities were predominant; multiple wounds were present in 30 per cent of cases*

We treated 26 severe abdominal wounds according to the established tactics in war surgery, with exteriorization and delayed closure of colon lesions, and primary suture of small bowel perforations[4,5]. Six lesions were in the retroperitoneum, with three severe lesions of the ureters and bladder. In 35 per cent of cases, more than one intra-abdominal organ was affected. These were 13 multiple lesions of the small bowel and 12 of the colon, 3 perforations of the diaphragm and 2 of the stomach, 1 lesion of the liver and 1 of the spleen. Two patients were admitted with an evisceration. The time of operations was measured for 212 patients who underwent 418 surgical procedures. Induction of anaesthesia and immediate postoperative recovery from anaesthesia were included. *Figure 3* shows the distribution of the different techniques used. Ketamine was preferred to regional anaesthesia in emergency operations because of its rapid action. All abdominal and thoracic operations were performed under anaesthesia with intubation and muscular relaxation.

Results

The duration of operations is shown in *Figure 4*. The average time was 90 min. Some operations lasted more than 180 min. Abdominal procedures were the longest, with an average of 180 min. Many patients had to undergo two or more operations. Debridement was nearly always followed by delayed closure and many wounds needed successive debridements and bone curettage. Two-staged procedures were generally adopted for colon lesions, the second operation usually being performed during a second hospital stay. The operative time was on average shorter for the second operation (55 min) than for the first (*Figure 4*).

War wounded stayed an average of 4 weeks in the hospital. Patients treated for thoracic and intra-abdominal lesions stayed a shorter period of time in the hospital (3 and 4·3 weeks) than those who sustained an amputation or an operation using an external fixator (5·2 and 5·8 weeks). General mortality was 2·8 per cent; it was higher for patients with abdominal and thoracic lesions (8·6 per cent and 12 per cent).

Discussion

Surgery for the treatment of war wounded differs widely in different conflicts and places. In recent wars missiles have been the most frequent cause of trauma; the differences observed in different wars are due to equipment and variations in evacuation facilities rather than to wounding agents[5–7]. Thus our analysis should contain useful information for medical activities in other conflicts.

Guerilla war can be considered in particular regarding its difficulty in transportation of war wounded: although close to the border, evacuation from the battlefield to the hospital was usually difficult. Nevertheless the time between injury and arrival at the hospital was, in 55 per cent of cases, within 24 h. Delayed admissions do not seem to have been associated with a modification in the distribution of the lesions, when compared with that observed in other conflicts[5,8,9]. This could mean that the proportion of death due to delays in transportation was the same in the different groups of patients, or that overall mortality was not influenced at all by the situation. This statement, although surprising, has been supported by an analysis of Howard and DeBakey who believed that care within 24 h keeps very few casualties from dying during the first 48 h: the majority of those who die of wounds probably die shortly after injury[10]. On the other hand, the low mortality rate observed in the ICRC hospital (2·8 per cent) could be explained by the selection produced by difficult transportation. This low mortality rate is however similar to the 2·4 per cent observed at the forward surgical hospitals during the Korean war[10].

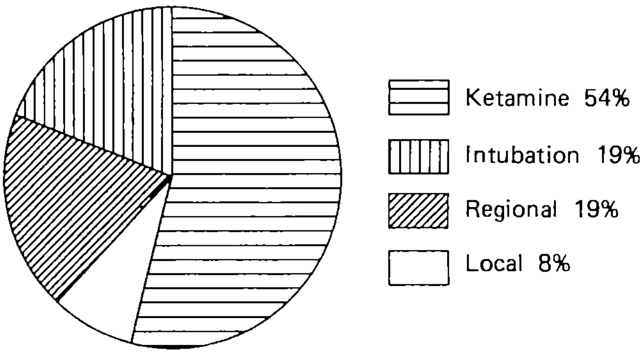

Figure 3 *Distribution of the different anaesthesias. General anaesthesia using ketamine was more frequently used than regional anaesthesia during operations to the extremities; general anaesthesia with intubation was used for abdominal and thoracic operations*

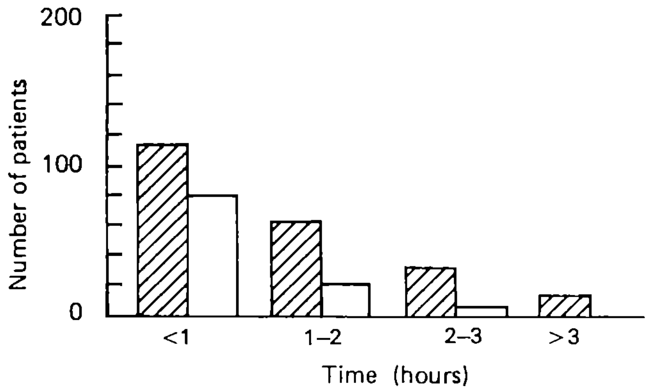

Figure 4 *Duration of the first operations (■, n = 212) (occupation of operating table) was on average 90 min. Most of them lasted less than an hour; operative time was over 2 h in 19 per cent of cases. Duration of the second operations (□, n = 108) averaged 55 min; only 6 per cent of them lasted more than 2 h*

There was an efficiency of treatment in spite of the simple hospital equipment. The duration of the first operations for the 212 patients was on average 90 min; many lasted more than 2 h. Treatment of 29 patients with intra-abdominal lesions needed on average 180 min per patient; these operations were long because of the associated injuries in 8 cases and because of the multiple intra-abdominal lesions in 35 per cent of cases. Our results are in agreement with previous estimates of operative time[10].

Wounds of the extremities required debridement and fracture stabilization with external fixator (18 cases) or traction (14 cases). Amputations were usually performed under difficult conditions, often in the presence of extensive infection due to delay imposed by initial refusal of the procedure, as observed in other conflicts in Islamic countries[11]. Mines inflicted severe lesions with frequent loss of a leg and extensively contaminated lesions of the other limbs sometimes associated with perineal and urethral lesions.

Treatment of these wounds was time consuming and could have been reduced, in cases of multiple lesions, by simultaneous work of two or more surgeons on the same patient.

The postoperative workload for the nursing team was on average lower for patients with abdominal or thoracic lesions than for those with lesions of the extremities, in whom dressings often had to be changed several times a day. The stay in the hospital was also shorter for patients with thoracic or intra-abdominal lesions than for those with fractures or amputations. Mortality, however, was higher for abdominal and thoracic lesions (8·6 per cent and 12 per cent) than for other injuries (average 2·8 per cent).

Overall the average time for hospitalized battle injuries was shorter (4 weeks) than in previous reports[10]; use of external fixators for treatment of fractures might explain this improvement.

Under circumstances of discrepancy between need and resources of operating facilities, the operative time should be kept as short as possible. Some armies have determined a maximal operating time of 60 min and planned their sanitary systems accordingly[1]. We believe that selecting patients under this time constraint would result in treating many minor cases who could survive without early surgery; patients with severe injuries, requiring longer operations would miss, if not treated, a real chance of survival. Such a policy of selection for operation would have withheld surgery to most of the patients in real danger in our cases.

In our experience, the long duration of an operation has not been correlated either with an unfavourable outcome or with an increased postoperative workload. We believe that in cases of massive admission of wounded and consequent overload of operating room facilities, all attempts should be made to accelerate the operative turnover by increasing the number of operative teams rather than by selecting for surgery cases likely to require short operative time.

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Short note

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External abdominal wall hernias: experience with elective and emergency repairs in Nigeria

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An analysis of 208 patients with 238 instances of external abdominal wall hernia repairs by one surgeon is presented. The overall mortality rate for hernia repair was 1·9 per cent. There were no deaths among 171 patients who underwent elective repairs, but the mortality rate for the 37 patients who had emergency repair of strangulated hernia was 11 per cent. In Nigeria, external abdominal wall hernias are a common cause of strangulated bowel obstructions and constitute the bulk of surgical emergencies. This study identifies those factors responsible for the delay in surgical repair of strangulated hernias and recommends solutions.

Patients and methods

Between August 1982 and July 1985, all cases of elective abdominal wall hernias were hospitalized 1 day before and discharged home 3 days after surgery. Patients with acutely incarcerated or strangulated hernias were resuscitated and operated upon within 4–8 h of admission.

Results

A total of 225 patients (186 elective and 39 emergencies) were seen within the 36-month period of this study. Of the 186 elective patients, 15 were not operated upon, either because they defaulted or because they had associated disease contraindicating surgery. Two of the 39 emergency cases died of toxaemia pre-operatively. Thus 208 patients (171 electives and 37 emergencies) were available for analysis.

Clinical features

Of the 208 patients operated upon for a total of 238 hernia repairs, the male to female ratio was 2:1 and the age range was 5 months to 85 years. *Table 1* summarizes the incidence of the various external abdominal wall hernias and *Table 2* shows the relationship of direct and indirect inguinal hernias with age. *Table 3* lists the reasons why patients sought medical help. Most adult patients had had their hernia for 5 years or more before consulting a doctor. Only three patients were found to have strangulation as the first evidence of hernia existence.

Table 1 *Frequency of the various external abdominal wall hernias by sex*

Types of hernia	Male	Female	Both sexes	Percentage of total cases
Right indirect	57	20	77	32·4
Left indirect	33	14	47	19·8
Right direct	30	17	47	19·8
Left direct	19	20	39	16·4
Umbilical	6	6	12	5·0
Epigastric	2	6	8	3·4
Femoral	2	4	6	2·5
Lumbar	1	0	1	0·4
Obturator	0	1	1	0·4
Total	150	88	238	100·0

Management and operative findings

The 171 patients in the elective group had uneventful hernia repairs.

Of the 37 emergency cases, 15 presented to the hospital 2 or more days after the onset of strangulation. These patients were febrile, severely dehydrated and toxic. They required more elaborate fluid and electrolyte resuscitation. Pre-operative antibiotic cover was provided consisting of 500 mg each of Ampiclox and metronidazole intravenously. Operative findings in this subgroup included massive peritoneal faecal soilage from ruptured gangrenous bowel in seven patients; frank gangrenous bowel without rupture in four and ischaemic but viable bowel in the remaining four cases. There were four postoperative deaths in this subgroup.

The remaining 22 patients in the emergency group presented to the hospital within 24 h of hernia strangulation. They were all operated upon within 4 h of admission as they required minimal resuscitative measures. Only one patient in this subgroup required bowel resection for non-viable ischaemic small intestine. None of these 22 patients died. The outcome for patients with strangulated hernias is given in *Table 4*.

Hospital stay

The average hospital stay for the 171 elective and the 25 patients in the emergency group who had no bowel resection was 2·5 days, but it was 13·9 days for the 8 cases who survived bowel resections owing to major postoperative wound infections in 4 patients.

Follow-up

The average follow-up is 20 months (range 8–44 months). Although there has been no documented case of hernia recurrence, one of the emergency cases who did not undergo bowel resection developed intestinal obstruction 1 month

Table 2 *The incidence of direct and indirect inguinal hernias with age*

Age	Percentage of direct inguinal hernias	Percentage of indirect inguinal hernias
Under 30 years	7·8	92·2
30–60 years	45·5	54·5
Over 60 years	77·8	22·2

Table 3 *Clinical features*

	Number of patients	
Reason for seeking medical advice	Elective	Emergency
Culturally unacceptable	89	0
Strangulation or acute incarceration	0	37
Presence of painful lump	30	0
Fear of infertility	26	0
Fear of strangulation	15	0
Cosmetic reasons	11	0
All patients	171	37

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Table 4 *Outcome of strangulated hernias*

	Bowel viable	Bowel gangrenous
Survivors (no.)	25	8
Deaths (no.)	0	4
Deaths (per cent)	0	33
Postoperative wound complication (no.)	0	4
Late complication (no.)	1	0

after discharge. On exploration a small bowel stenosis was found at the site of the earlier strangulation. He recovered following resection of the stenotic portion with an end-to-end anastomosis.

Discussion

In Port Harcourt, Nigeria, external abdominal wall hernias, a predominantly male disease, constitute a major health problem which is often overlooked because no study has focused on the high morbidity and mortality resulting from delayed surgical repair of strangulated hernias.

The majority of the emergency cases in this study came from the rural areas of the state where health facilities are inadequate and transportation is difficult. Usually poor and ignorant, these patients were unable to afford the high cost of medical treatment in urban health centres. Some resorted to protracted ineffective treatment by native doctors or 'quacks' and came to hospital moribund often days after hernia strangulation had occurred.

In the present study there was no mortality among 171 patients who had elective hernia repairs. Similar results were reported by Tingwald and Cooperman[1] and Flanagan and Bascom[2] in their series of 44 and 303 patients respectively.

The mortality rate for hernia repair in this report is 1·9 per cent and is entirely due to the mortality rate of 11 per cent from the repair of strangulated hernias. The mortality rate resulting from the repair of strangulated hernias when gangrenous bowels were resected was 33 per cent. Similar mortality rates were reported by Tingwald and Cooperman[1], 22 per cent; Leffall and Syphax[3], 30 per cent; and Archampong *et al.*[4], 20 per cent. The incidence of hernia strangulation in this study was 15·6 per cent; and the rate of bowel resection following hernia strangulation was 32·4 per cent. The rate of bowel resection when surgical repair was delayed 2 or more days was 73·3 per cent (twice the rate for the entire emergency cases). Surgical repair carried out within 24 h of hernia strangulation reduced the rate of bowel resection to 4·5 per cent (16 times less than the rate when repair was delayed). The mortality rate following early surgical repair is also reduced from 33 per cent to zero, indicating a direct relationship between delayed repair, bowel resection and mortality for strangulated hernias.

The above analysis shows that elective hernia repair is an effective preventive medical practice which should be adopted, particularly in the developing countries where poverty, ignorance and inadequate health facilities hamper early surgical intervention when hernia strangulation occurs.

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Appraisal of hepatic resection in the treatment of minute hepatocellular carcinoma associated with liver cirrhosis

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During the last 6 years, 205 patients with primary hepatocellular carcinoma (HCC) were admitted to our surgical departments. Thirty-eight had HCC smaller than 3 cm in diameter. There were 34 men and 4 women with an average age of 56·5 years. All patients had underlying hepatic disease: liver cirrhosis in 35 patients and chronic active hepatitis with fibrosis in the remaining 3. Pre-operative complications included: oesophageal varices in ten, cholelithiasis in five, peptic ulcer in two, gastric cancer in one, and severe hypersplenism in one instance. A radical resection was performed in 32 cases and palliative resection in 6. Simultaneous operations were carried out for the above mentioned associated conditions: distal splenorenal shunt in six, Hassab's devascularization procedure in one, splenectomy in one, cholecystectomy in four, cholecystolithotomy in one, and partial gastrectomy in one. Four patients had postoperative complications: liver failure, rebleeding, right haemothorax, and upper gastrointestinal bleeding from acute mucosal lesion of the stomach. One patient with liver failure died in coma within 1 month. The operative and in-hospital mortality rates were 2·6 and 7·9 per cent, respectively. Survival rates during the first 4 years in 32 patients with radical hepatic resection were 89·9, 67·2, 58·8, and 58·8 per cent, respectively. We suggest that hepatic resection should be the first choice of treatment for minute HCC even in the presence of liver cirrhosis.

Keywords: Hepatocellular carcinoma, liver cirrhosis, minute hepatoma, hepatic resection, natural history

Despite recent advances in diagnostic methods for hepatocellular carcinoma (HCC), its prognosis is generally poor[1,2]. The low resectability of HCC is probably accounted for by a high incidence of associated liver cirrhosis or the malignant nature of this tumour with invasion of the portal or hepatic veins or early spread to the entire liver. It is well known that cirrhotic livers are less able to regenerate and therefore that major hepatic resection is contra-indicated in the presence of advanced liver cirrhosis[3]. However, the incidence of small HCCs has recently increased due to a thorough follow-up of patients with chronic liver disease using measurement of serum α-fetoprotein (AFP) level, ultrasonography, or computed tomography[4,5]. We have shown that HCCs, thus discovered at a preclinical stage, are often resectable even in the presence of liver cirrhosis[6–8].

Until recently, we were uncertain if an aggressive resection of small HCCs with advanced cirrhosis was beneficial, but Ebara *et al.*[9] clearly presented the natural history of 22 cirrhotic patients with HCCs smaller than 3 cm. In this communication, we report the results of hepatic resection in 38 patients with minute HCCs associated with liver cirrhosis and further compare them with the natural history of similar patients reported by them.

Patients and methods

From January 1980 to December 1985, 205 patients with primary hepatocellular carcinoma (HCC) were admitted to our surgical departments. Thirty-eight (18·5 per cent) had HCCs smaller than 3 cm in maximum diameter. There were 34 men and 4 women. Age ranged from 34 to 72 years with an average of 56·5. Diagnosis was made by serum AFP elevation in 17, serial ultrasonographic examination during the follow-up of chronic liver disease in 14, and precise examination of liver cirrhosis or oesophageal varices in 7 cases. Thirty-six patients had a history of chronic liver disease of 1–35 years. Alcohol abuse was noted in half of the patients. Only two patients had a history of blood transfusion. Hepatitis B surface (HBs) antigen was positive in only seven patients but anti-HBc (core antigen) was positive in 70·3 per cent of the patients. Eighty per cent were positive for at least one of HBs-antigen, anti-HBs, or anti-HBc (*Table 1*).

Pre-operative liver tests and tumour markers

Serum activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were slightly elevated in most of the patients. The AST/ALT ratios were between 0·4 and 2·5. Total bilirubin level was within the normal range in 23 instances. Serum albumin was lower than normal in a half of the patients but they were all above 30 g/l. Both bromosulphalein and indocyanine green retention rates, on the contrary, showed higher values than normal in most patients. Twenty-six had Child's class A, eleven had class B, and one had class C liver disease. Serum AFP level was below 1000 ng/ml in 28 patients, 18 of whom had values lower than 100 ng/ml. There were only five patients whose AFP level was higher than 2000 ng/ml. Serum ferritin levels were elevated in approximately half of the patients. Serum carcinoembryonic antigen was slightly elevated in 13 cases but remained within the normal range in the remaining patients.

Table 1 *Clinical data of 38 patients with minute HCC*

Data		Number (%)
Alcohol abuse		
Yes		19 (50·0)
No		19 (50·0)
Blood transfusion		
Yes		2 (5·3)
No		36 (94·7)
HBV profile		
Hepatitis B surface antigen	(+)	7 (18·9)
	(−)	30 (81·1)
Anti-hepatitis B surface antigen	(+)	5 (13·5)
	(−)	32 (86·5)
Anti-hepatitis B core antigen	(+)	26 (70·3)
	(−)	11 (29·7)

Numbers in parentheses are percentages. Alcohol abuse was considered to be consumption in excess of 50 g/day for > 5 years. HBV profile was measured by radio-immunoassay

Pre-operative imaging studies

Thirty-two patients had a solitary HCC not larger than 3 cm in maximum diameter. However, five patients had two and one patient had three HCC nodules smaller than 3 cm. Thus, there were 45 HCCs in the 38 patients. The detectability of these 45 tumours was 82·2 per cent by ultrasonography, 84·4 per cent by computed tomography, and 88·9 per cent by selective arteriography.

Associated liver disease and other conditions

Liver cirrhosis was confirmed macro- and microscopically in 35 patients: micronodular in 14, macronodular in 9, and mixed type cirrhosis in 12. Three patients had chronic active hepatitis with moderate fibrosis. A total of 36 associated disorders were present in 27 patients: diabetes mellitus in 15, oesophageal varices in 10, cholelithiasis in 5, peptic ulcer in 2, gastric cancer in 1, submucosal tumour of the stomach in 1, severe hypersplenism in 1, and chronic alcoholism in 1.

Operative methods

In 32 patients with a solitary HCC nodule, the tumours were extirpated by left lateral segmentectomy in 2, by other segmentectomies in 4, and by partial wedge resection in 26. Five patients with two HCCs in different segments or lobes of the liver had these resected separately by two wedge resections. In the patient with three HCC nodules, removal was by two partial hepatectomies. The operations were considered radical in 32 instances but only palliative in the remaining 6. These judgements were made by intra-operative findings and immediate postoperative evaluation of all the patients by ultrasonography, computed tomography, AFP measurement, and if necessary angiography. The following operations were simultaneously performed with hepatic resection in the treatment of the associated conditions: distal splenorenal shunt in six, devascularization of the stomach and splenectomy in one, splenectomy in one, cholecystectomy in four, cholecystolithotomy in one, and partial gastrectomy in one case.

Results

Postoperative morbidity and mortality

Four patients had postoperative complications: liver failure, postoperative rebleeding, right haemothorax, and upper gastrointestinal bleeding from acute mucosal lesion of the stomach, respectively. Those with the latter three complications were successfully treated by conservative methods, but the patient with liver failure died in coma on the sixth postoperative day. Two patients died 3 months after operation without discharge from hospital; one due to hepatic failure and the other due to renal failure. The operative and in-hospital mortality rates were thus 2·6 and 7·9 per cent, respectively. The simultaneous operations did not cause complications.

Histology of liver and tumour

All patients had underlying hepatic disease: liver cirrhosis in 35 (14 micronodular, 9 macronodular, and 12 mixed type) and chronic active hepatitis with moderate fibrosis in 3 cases. A pseudocapsule around the HCC was found in 28 patients. The microscopic appearance was trabecular in 32, pseudoglandular in 1, mixed type of trabecular and clear cell in 4, and mixed type of trabecular and pseudoglandular in 1 case. The grade of tumour differentiation was grade II in 18, grade III in 6, and mixed in 14 patients.

Survival

Thirty-five patients were discharged from hospital. At present, 25 patients are alive, 20 being free of cancer and 5 with tumour recurrence. Ten patients died after discharge due to tumour recurrence in seven and liver failure in three cases. There were no deaths from variceal bleeding. *Figure 1* shows the cumulative survival rate (Kaplan–Meier method) in 32 patients with radical (group A) and 6 patients with palliative resection (group B). Survival rates during the first 4 years in group A were 89·2, 67·2, 58·8, and 58·8 per cent, respectively. The 2-year survival rate was 20·0 per cent for group B.

Comparison with natural history of similar patients

Recently, Ebara *et al.*[9] in Chiba University, Japan reported the natural history of 22 cirrhotic patients with HCCs smaller than 3 cm. *Figure 2* illustrates a comparison between our 32 patients with radical hepatic resection (group A) and the 22 patients from Chiba University (group C). A significant

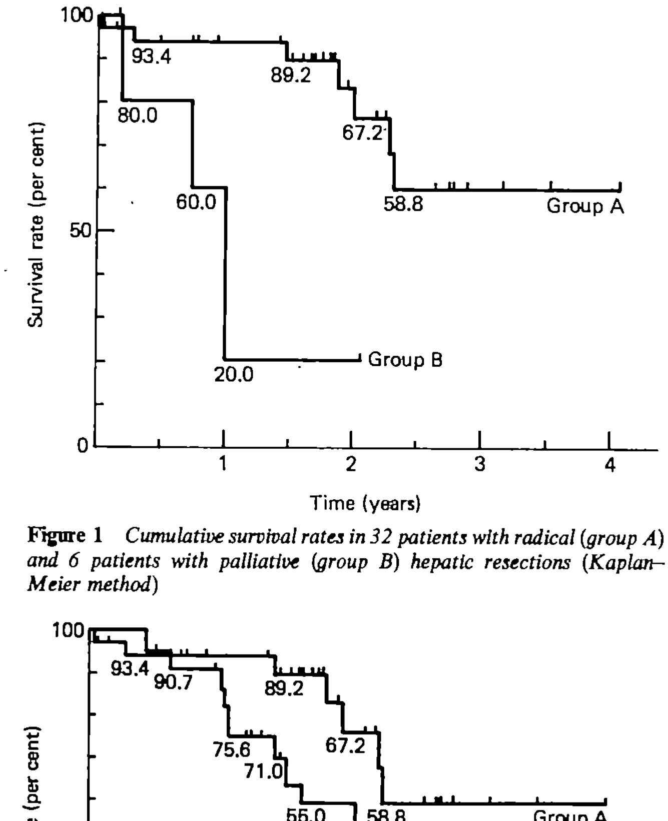

Figure 1 *Cumulative survival rates in 32 patients with radical (group A) and 6 patients with palliative (group B) hepatic resections (Kaplan–Meier method)*

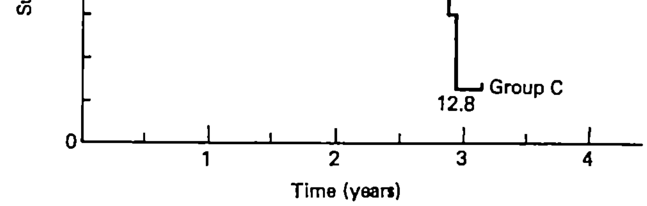

Figure 2 *Comparison of cumulative survival rate between 32 patients with radical hepatic resection (group A) and 22 patients with cirrhosis and HCC smaller than 3 cm (group C). The survival curve of group C was used by permission of Dr Ebara* et al.

difference is seen in survival rate after three years (58·8 per cent for group A *versus* 12·8 per cent for group C).

Discussion

Although cirrhotic livers are less able to regenerate and accordingly major hepatic resection is usually contra-indicated in the presence of liver cirrhosis[3], this is not necessarily true for all cirrhotic patients. As we have recently reported[7,8], selected patients with associated cirrhosis tolerate a major hepatic resection. Since most HCCs in Japan develop in livers with chronic parenchymal disease, particularly with cirrhosis[1], every effort should be undertaken to obtain a higher resectability of HCCs. There can be two approaches: a close follow-up of the patients with chronic liver disease with the aid of AFP measurements, ultrasonography, computed tomography, and selective arteriography[4–6] and a proper evaluation of hepatic functional reserve of cirrhotic livers both qualitatively and quantitatively in order to assess the safe extent of hepatic resection in an individual patient[10,11].

In the present series of patients, we lost one patient in the first postoperative month and two patients 3 months after hepatectomy during their initial stay in hospital. The operative and in-hospital mortality rates were therefore 2·6 and 7·9 per cent, respectively. During the last 6 years our policy has been to treat small HCCs in the cirrhotic liver by resection; however, we were uneasy that aggressive resections really achieved improved overall survival. Although the clinicopathological background was similar in the patients reported by Ebara *et al.*[9] and our patients, the current investigation clearly demonstrated the significance of radical hepatic resection in the treatment of minute HCC with cirrhosis. The 4-year survival rate in 32 patients with radical resection is more than we expected.

Thus, the current study indicates that serial estimation of serum AFP level and serial ultrasonographic study will detect HCC in patients with chronic liver disease, that hepatic resection can be safely performed in the patients with HCCs discovered in this way, and that the survival rate in these patients with radical hepatic resection is significantly superior to the natural history of similar patients. We conclude that hepatic resection should be the first choice of treatment for minute HCC even in the presence of liver cirrhosis.

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Role of surgery in the treatment of primary carcinoma of the liver: a 31-year experience

During the 31 year period 1954 to 1985, 225 major hepatic resections have been performed for symptomatic primary carcinoma of the liver, of which right hepatic lobectomy was performed in 115, extended right hepatic lobectomy in 11, trisegmentectomy in 2, left hepatic lobectomy in 94, and middle hepatectomy in 3. In addition there were 107 partial hepatic resections for 89 asymptomatic small hepatocellular carcinomas. In the 225 patients undergoing major hepatic resection, the operative mortality was 8·0 per cent. In the 107 patients undergoing partial hepatic resection, the operative mortality was 5·6 per cent. Of the total of 314 hepatic resections for primary carcinoma of the liver, 309 were undertaken for hepatocellular carcinoma and the remaining 5 were carried out for cholangiocarcinoma. All hepatic resections in this series were performed with the finger fracture technique without controlling the hepatic hilar vessels, hepatic ducts or hepatic veins outside the liver, although hepatic clamping and the Pringle manoeuvre were also used in selective cases. Of 207 cases who survived major hepatic resection, 119 cases died within one year after the operation, mainly due to recurrence of cancer in the remaining residual lobe, lung metastasis or late hepatic failure. The 5 year survival rate is 18·0 per cent, 12 patients are still alive and well after more than 5 years and the longest survival is 23 years. Of the 89 patients with small asymptomatic hepatocellular carcinomas, 28 died within one to four years of surgery because of a second new growth.

Keywords: Liver surgery, hepatocellular carcinoma, cirrhosis

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Surgical resection has been adopted as the main treatment of hepatic tumours over the past decade with improvement in our understanding of hepatic anatomy and physiology. The main indications for hepatic resection are benign hepatic tumours, primary malignant tumours particularly hepatocellular carcinoma (HCC), and metastatic hepatic tumours. Hepatic resections have been performed more frequently for HCC in Asian countries[1–6] than in the Western hemisphere[7–10] because of the geographical preponderance of HCC in Asia. During the 31 year period from March 1954 until October 1985, 752 patients with primary carcinoma of the liver have been dealt with in the Department of Surgery, National Taiwan University Hospital. Of these, 314 patients have undergone hepatic resection.

This report reviews our experience of the surgical management of primary carcinoma of the liver and describes the pre-operative investigation, the indications for hepatic resection, the modification of surgical technique and the results of surgery.

Patients and methods

During the 31 year period, 314 hepatic resections for primary carcinoma of the liver were performed by the authors, of which 309 were undertaken for HCC and 5 for peripheral cholangiocarcinoma. Benign hepatic tumours and other types of primary or metastatic liver malignancy have been excluded from this review.

Among 225 major hepatic resections for symptomatic primary liver cancer, right hepatic lobectomy was performed in 115, extended right hepatic lobectomy in 11, trisegmentectomy in 2 and middle hepatectomy in 3. Of these 131 patients, 107 were non-cirrhotic and 24 were cirrhotic. Left hepatic lobectomy was performed in 94 patients, of whom 56 were non-cirrhotic and 38 were cirrhotic. In the hepatic lobectomy group, there were 3 *en bloc* resections of the right hepatic lobe plus partial resection of diaphragm, retroperitoneum and colon, and one other *en bloc* resection of the left hepatic lobe plus resection of omentum and stomach.

In 89 patients with asymptomatic small HCC (2–3 cm in size), 107 partial hepatic resections have been performed since 1979, although 80 per cent of these patients had liver cirrhosis.

Of 314 hepatic resections for primary carcinoma of the liver, 271 were undertaken in male patients. Sixteen of the 314 patients were less than 15 years old. The average age of the adult patients was 53 years (range 19–73 years).

Pre-operative investigation

In an area such as Taiwan where the incidence of HCC is high, the diagnosis was always considered when a hepatic mass was palpated or non-coagulable blood was aspirated from the abdominal cavity in patients with an acute abdomen but no history of trauma. Routine diagnostic tests include α-fetoprotein determination, radioisotope liver scanning (for symptomatic patients), hepatic ultrasonography and computerized tomography (for asymptomatic patients) and peritoneoscopy. Selective hepatic arteriography was not used routinely.

Percutaneous liver needle biopsy was not performed merely to establish the diagnosis before operation in that, regardless of whether the tumour is benign or malignant, hepatic resection is the only satisfactory method of treatment. The five patients with peripheral cholangiocarcinoma in this series presented with clinical findings similar to those of HCC and the pathological diagnosis was obtained from the resected specimen. Peritoneoscopy was performed to assess the presence of hepatic cirrhosis and detect tumour nodules elsewhere in the liver.

Indication for operation and hepatic resection

From 1954 to 1969, we had a particularly active attitude towards laparotomy in an attempt to increase operability rates and as a way of facilitating other surgical procedures such as hepatic artery ligation or transhepatic arterial chemotherapy when the tumour was unresectable. Since 1970 we have abandoned this attitude in patients thought to be unresectable after pre-operative evaluation since it has become evident

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Table 1 *Intra-operative complications and operative mortality in 225 patients undergoing major hepatic resections for symptomatic primary liver cancer*

Intra-operative complications	109 cases (1954–1970) No.	Deaths	116 cases (1970–1985) No.	Deaths
Cardiac arrest	6	2	0	0
Kinking of vessel and duct of contralateral lobe	1	1	0	0
Ruptured bleeding HCC	1	1	0	0
Fibrinolysis	3	3	1	1
Vena cava tear	2	0	1	0
Bleeding from collaterals	0	0	3	2
Other deaths within 30 days of operation				
Cancer embolization to brain		1		0
Hepatic failure		3		2
Varices rupture		1		1
Operative mortality (death within 30 postoperative days)	12/109 (11·0%)		6/116((5·1%)	

that neither transhepatic arterial chemotherapy nor hepatic artery ligation have been effective. Furthermore, the incidence of postoperative hepatic failure has been unacceptably high among cirrhotic patients after hepatic lobectomy (see below).

At present we have the following indications for hepatic resection in patients with cirrhosis. (1) Hepatic lobectomy is indicated for the right or the left lobe if the cancer free lobe is macroscopically normal. (2) In the presence of moderately advanced cirrhosis with a coarse nodular liver surface, hepatic lobectomy of the left, but not the right lobe, can be performed. (3) In cases with advanced cirrhosis, hepatic lobectomy for either lobe is contra-indicated. In cases of asymptomatic small HCC, partial hepatic resection can be performed without jeopardizing liver function in cirrhotic patients[11]. However, partial resection may induce hepatic failure if a nodule larger than 5 cm close to the hilar area in the right lobe is removed or more than three nodules are removed at the same time.

Surgical technique

During the 31 year period, all of our hepatic resections for primary carcinoma of the liver were performed using the finger fracture technique without controlling or routinely occluding the hepatic hilar vessels or hepatic veins outside the liver[12,13]. With this technique the hepatic lobectomy is simplified and operation time is reduced by omitting the isolation of the ductalvascular system at the porta hepatis and of the hepatic veins near the vena cava.

In 113 patients undergoing major resection we have used a hepatic clamp (Takasago Medical Industry Co. 33-4, 2 Chome, Takasago, Katsushika-Ku, Tokyo, Japan) applied to the boundary between two hepatic lobes to reduce bleeding from the cut surface of the liver. If blood transfusion is needed in such patients, it is usually because of the separation of adhesions to the diaphragm or retroperitoneum. In cirrhotic patients these adhesions are highly vascular and two to five litres of blood may have to be transfused. Oozing of blood from such raw surfaces is difficult to deal with, but applications of Avitene Powder (microfibrillar collagen haemostate; Aricos Inc. Fort Worth, TX, USA) with compression has been used to help to provide haemostasis.

Among the 225 major hepatic resections, 109 cases were operated upon with the original finger fracture technique alone, 102 cases with finger fracture and hepatic clamping[14], 11 cases with the crush method and hepatic clamp[15] and 3 cases of middle hepatectomy were performed using finger fracture and the Pringle manoeuvre. The other 107 partial hepatic resections for 89 asymptomatic small HCC were performed with the finger fracture technique using either a hepatic clamp or temporary clamping of hepatic artery.

If the hepatoma is located in the lateral portion of the right lobe but is already invading the diaphragm, retroperitoneum, omentum or colon or when there is a ruptured hepatoma which has been sealed off by the adjacent structures with vascular adhesion, we have amputated the hepatic lobe first by finger fracture and hepatic clamping. The cancer bearing lobe is then removed in a retrograde manner with partial resection of diaphragm, omentum, retroperitoneum or colon en masse using a coagulator and without disturbing the vascular adhesions or area of cancer invasion[16].

Mattress sutures are placed among the cut edge of the liver in partial resection, but are seldom used in lobectomies. After lobectomy the raw surface of the liver is left open and covered with omentum. A T-tube was not inserted in the common bile duct.

A bilateral subcostal incision was routinely used with right thoracic extension through the eighth intercostal space in the period 1954 to 1968 for right hepatic lobectomy or extended right hepatic lobectomy in adult patients. Children less often required thoracotomy, but if necessary the costal margin was divided in children older than 13. Since 1969, only a bilateral subcostal incision with upper midline extension to the xiphoid process (the xiphoid process is not excised) was used for right or left hepatic lobectomy. Right thoracic extension has only been used occasionally for a huge right hepatoma or when partial resection of diaphragm or *en bloc* resection is intended. A chest tube was inserted into the thoracic cavity when the chest had been opened. Two Penrose drains were placed in the subphrenic space on the side of resection.

Results

Intra-operative complications and operative mortality

The intra-operative complications and deaths in the 109 major hepatic resections performed between 1954 and early 1970 with the finger fracture technique are shown in *Table 1*. Of the six patients with major intra-operative bleeding, one with a ruptured bleeding hepatoma died in the operating room, three developed fibrinolysis immediately following hepatic lobectomy and died on the first postoperative day. The vena cava was torn in two cases during operation, but the bleeding was controlled by vascular suture after applying a Satinski vascular clamp.

Cardiac arrest occurred in 6 of the 12 infants and children during hepatic lobectomy. Two died of brain anoxia and renal failure on the first postoperative day. In the other four, the cardiac arrest was detected promptly and after resuscitation the patients survived the operation.

Five more patients succumbed within 30 days of operation because of hepatic failure (three cases), ruptured oesophageal varices (one case) and suspected cerebral cancer embolization (one case). Therefore, the 109 cases had an operative mortality rate of 11·0 per cent.

The intra-operative complications in the 116 major hepatic resections performed between late 1970 and 1985, during which the operations were carried out by finger fracture or the crush method combined with hepatic clamping or the Pringle manoeuvre, are shown in *Table 1*. The vena cava was torn in three places in one case, but this was controlled by applying a Satinski clamp followed by vascular suture. One patient died of fibrinolysis on the first postoperative day. Bleeding from collaterals developed in three cirrhotic patients, one of whom underwent reoperation for control of bleeding by suturing the diaphragmatic surface. The other two patients died of hepatic failure on the second postoperative day even though the bleeding had been controlled by conservative means. Two other

Table 2 *Postoperative complications in 225 patients undergoing major hepatic resection for primary liver cancer*

Complication	No. of patients Non-cirrhotic	Cirrhotic
Pleurisy	12	3
Unknown fever	10	3
Bile leakage	4	0
Subphrenic abscess	4	0
Pneumonia	1	0
Reactivated lung tuberculosis	2	0
Wound infection	1	1
Cystitis	1	0
Gastrointestinal bleeding	2	0
Ascites	0	10
Ankle oedema	0	12
Jaundice	0	2
Varices rupture	0	2

Table 3 *Relationship between cirrhosis and hepatic failure after major hepatic resection for primary liver cancer (222 cases*)*

	Non-cirrhotic		Cirrhotic	
	Resection No. of cases	Hepatic failure No. of cases (%)	Resection No. of cases	Hepatic failure No. of cases (%)
Right hepatic lobectomy	106	6 (5·6)	22	13 (59)
Left hepatic lobectomy	56	0 (0)	38	6 (15·8)
Total	162	6 (3·7)	60	19 (31·7)

* Patients undergoing middle lobectomy have been excluded from this Table

patients died of hepatic failure and one died of variceal rupture within 30 days of operation, giving an operative mortality of 5·1 per cent in this later series.

A total of 18 deaths in the 225 major hepatic resections gives an overall operative mortality of 8·0 per cent.

In the 107 partial hepatic resections performed in 89 patients with asymptomatic small HCC, none died of hepatic failure even though 80 per cent of them were cirrhotic. There was one intra-operative death due to bleeding and six deaths within 30 days after surgery were attributable to myocardial infarction (one case), fulminating hepatitis (one case) and ruptured oesophageal varices (four cases).

Postoperative complications

Complications were relatively uncommon in non-cirrhotic patients (*Table 2*). Ten patients had a fever (> 38°C) of unknown origin that was readily controlled by prednisolone. A light bloody discharge from the subphrenic tube for a few days was common but usually sealed spontaneously. There were four instances of bile leakage which lasted for more than two weeks. One of these patients developed a permanent external biliary fistula that was dealt with by anastomosis to a Roux-en-Y jejunal loop.

In the cirrhotic group, more serious complications such as ascites, ankle oedema, pleurisy or jaundice were frequently observed, particularly in those who underwent right hepatic lobectomy. In the patients undergoing major resection, cirrhosis was a major determinant of liver failure in the postoperative period (*Table 3*).

Survival

Of the 207 patients who survived major hepatic resection, 119 died within one year and 24 died between one and two years after operation. The main causes of death within two years are shown in *Table 4*. Thus, of the patients leaving hospital, 39·3 per cent survived more than 1 year, 25·0 per cent for more than 2 years, 18·5 per cent for more than 3 years, and 18·1 per cent for more than 5 years. At present we have 12 patients who are alive and well after 5–23 years.

In the group of 107 partial hepatic resections in 89 patients with asymptomatic small HCC, 28 died because of a second new growth between 1–4 years after the operation. There are 54 patients still alive, 19 having survived for 1 year, 8 for 2 years, 10 for 3 years, 10 for 4 years, 4 for 5 years and 3 for more than 5 years.

Discussion

The average length of time from onset of symptoms of HCC to death is as short as 4 months in Taiwan. As patients usually seek medical care some 2 months after the onset of their symptoms, the precious 2 months left in their lives should not be wasted on unnecessary pre-operative investigation which may lose the chance of effective treatment. Usually we complete our pre-operative diagnostic procedures in a week, and proceed at once to surgery in cases thought to be operable.

Along with measurement of serum α-fetoprotein levels, computerized tomograpy and hepatic ultrasonography have played important roles in the early detection of asymptomatic small HCC and are able to demonstrate tumours as small as 2 to 3 cm in diameter. The nodular shadow which appears on sonography may be hyperechoic, hypoechoic and even isoechoic in appearance. To determine whether the shadow is due to HCC may then require arteriography to demonstrate tumour circulation. Our 89 asymptomatic small HCC patients were detected by periodic examinations of α-fetoprotein levels and hepatic sonography among HBsAg carriers and also from periodic examinations of cirrhotic patients by hepatic sonography.

Table 4 *Causes of late death in 207 patients surviving major hepatic resection for primary carcinoma of the liver (1954–1985)*

Cause of death	No. of patients
Within 2 years of operation (143 patients)	
Cancer in residual lobe	81
Lung metastasis	16
Recurrence + lung metastasis	4
Hepatic failure	22
Intracranial involvement	1
Massive gastrointestinal bleeding	1
Unknown	18
Within 3–8 years of operation (13 patients)	
Cancer in residual lobe	7
Cirrhosis	3
Unknown	3

Operation is contra-indicated in HCC patients with lung and/or bone metastasis, with severe jaundice or ascites, with poor liver function and poor general condition. In the selection of patients for surgery, the presence or absence of associated liver cirrhosis must also be taken into consideration, particularly when right lobectomy is to be performed. Hepatic failure is common in such patients due to the deterioration of liver function and the absence of regeneration of the liver remnant[17,18]. At present we do not perform right lobectomy in patients with coarse nodular liver cirrhosis. However, it is wrong to judge a patient's tumour as inoperable simply on the basis of the histological demonstration of cirrhosis by needle biopsy. We have one patient who survived for 8 years after left hepatic lobectomy for HCC even though her liver showed histological cirrhosis. Three other patients with HCC combined with coarse nodular cirrhosis have survived for 2–4 years after left hepatic lobectomy. Bleeding from the vena cava is a potentially important problem. None of our three patients with caval tears died as our finger fracture technique divides the hepatic lobe from above downwards, so that the tears could be easily compressed digitally followed by application of a Satinski clamp and suture. The most serious and life threatening bleeding problem is fibrinolysis and none of the available treatments are effective when fibrinolysis becomes established. Early detection of fibrinolysis by frequent checks on blood coagulation during hepatic lobectomy is vital.

Regarding bile leakage, some authors recommended intra-operative cholangiography to identify potential leaks and ductal kinking[8], or inject saline through a T-tube in the common bile duct to detect open bile ducts at the cut surface of the liver[7]. Although we do not insert a T-tube we have encountered only one patient in whom a permanent biliary fistula developed.

Ruptured HCC is still curable by hepatic lobectomy. In patients with unresectable ruptured HCC, hepatic artery ligation is the best way to stop the bleeding. If the patient's condition does not allow laparotomy, transcatheter embolization of hepatic artery may be effective[19].

The long term results in our 225 patients having major hepatic resection have not been very satisfactory. Most of the deaths within two years of resection were due to recurrence of cancer in the residual liver. However, the main cause of late death in those who survived for 3 to 8 years after hepatic lobectomy was also recurrence in the remaining lobe (*Table 4*). Early recurrence is presumed to be due to pre-existing intrahepatic spread which becomes manifest 1 to 2 years later. Late 'recurrence' of cancer 3 to 8 years after surgery is probably not due to intrahepatic metastasis but to a new hepatoma in the remaining lobe.

The incidence of asymptomatic HBsAg carriage is high in Taiwan. Of our HCC patients 87 per cent are HBsAg positive and in 80 per cent of the patients following resection, the presence of HBsAg was proved by Orcein stain (W. S. J. Lin, personal communication), implying that even after resection our patients still have chronic hepatitis B. According to the literature, the end results of major hepatic resection for primary liver cancer are worse in Asian countries[2,4,6] than Western countries[7–9]. The reason for this difference is not clear. However, the fact that the majority of our patients have chronic hepatitis and may have aflatoxin contaminated food could contribute to the growth of new HCC. Progression of hepatitis into cirrhosis may have occurred due to the repeated acute exacerbation of hepatitis and that could also be responsible for the higher incidence of late deaths in Asian countries. From this evidence, it seems that hepatic resection still plays an important role in the treatment of primary carcinoma of the liver. However, the relatively high incidence of death within one year of surgery is perhaps attributable to metastasis to the contralateral lobe via the portal vein, and in three of our patients cancer thrombus was evacuated from the portal vein at surgery. With the availability of intra-operative ultrasonography it would seem advisable to seek deep seated metastatic nodules within the contralateral lobe before lobectomy.

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Renal impairment following biliary tract surgery

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Postoperative mortality has been directly attributed to renal failure in approximately 5 per cent of patients after surgery for obstructive jaundice. An analysis of 334 patients undergoing biliary tract surgery was undertaken to identify the perioperative factors associated with the development of renal impairment, and to estimate the contribution of renal failure to mortality. Thirty-eight patients (11 per cent) developed postoperative renal impairment (a two-fold increase in serum creatinine postoperatively or a rise of >100 *μmol/l). Ninety-three factors were examined in these and 196 control patients. Stepwise logistic regression analysis identified only three factors which were significantly associated with renal impairment: postoperative sepsis* ($P<0{\cdot}0005$)*, pre-operative serum bilirubin* ($P<0{\cdot}0005$)*, and pre-operative urea* ($P<0{\cdot}05$)*. Renal impairment developed at a median 4 days after surgery and was associated with a median of two additional major postoperative complications, particularly sepsis and haemorrhage, for which 17 patients underwent reoperation. Twenty-eight (74 per cent) of the patients with renal impairment died in hospital, but in only one case was the cause of death directly related to renal failure. Twenty patients received specific therapy for renal failure, but only one of these survived. Pre-operative obstructive jaundice and postoperative infection are the major factors associated with renal impairment after biliary tract surgery. Renal impairment appears to be related to postoperative complications rather than directly to the surgical procedure itself. The development of postoperative renal impairment predicts a low chance of survival but appears to be an indicator, rather than a direct cause of a poor prognosis.*

Keywords: Biliary tract disease, extrahepatic cholestasis, acute kidney failure, multiple organ failure, postoperative complications, regression analysis

Postoperative mortality has been directly attributed to renal failure in approximately 5 per cent of patients undergoing surgery for obstructive jaundice[1–4]. Indeed up to 22 per cent of these patients develop postoperative renal impairment[4–9]. The incidence of postoperative renal problems appears to have changed little over the past 20 years, despite improvements in perioperative management, and the regular use of mannitol infusions as suggested by Dawson[10].

The aims of this study were:

1. To assess the current incidence of renal impairment following biliary tract surgery in a specialist hepatobiliary unit.
2. To identify the perioperative factors which were associated with the development of this complication.
3. To estimate the contribution of renal failure to postoperative mortality.

Methods

Patients

During the period May 1979 to October 1985, 334 patients underwent biliary tract surgery on the Hepatobiliary Unit, Hammersmith Hospital. This group included all patients undergoing surgery to the intra- or extrahepatic bile ducts apart from those having surgery for acute or chronic pancreatitis (other than for gallstone-related disease), hepatic resection for conditions other than primary biliary tract disease or simple cholecystectomy. Patients who developed renal impairment requiring treatment before surgery were not included in the subsequent analysis.

Perioperative management

Particular care was taken to ensure that all jaundiced patients were well hydrated pre-operatively, and these patients received an infusion of 200 ml of 10 per cent mannitol commencing immediately before surgery. Throughout the period of this study, broad spectrum antibiotic prophylaxis was given to all patients both before invasive biliary investigations and immediately before surgery. In general, a three dose regimen was used for surgical prophylaxis: one dose at induction of general anaesthesia, with further doses 8 and 16 h later. Cephamandole (1 g, 500 mg, 500 mg IV), tobramycin (120 mg, 80 mg, 80 mg IV), and metronidazole (500 mg IV × 3) were used during the period May 1979 until April 1983, and piperacillin (4 g IV × 3) and tobramycin (as above) were used from May 1983 onwards.

Patient groups

Of the 334 patients 38 (11 per cent) developed postoperative renal impairment, which was defined as a two-fold increase in the pre-operative serum creatinine or an increase in serum creatinine of at least 100 μmol/l. In general serum creatinine was measured on the first two postoperative days and then at least twice weekly until discharge or death. Two hundred control patients were selected randomly from the group of patients who underwent biliary tract surgery but did not develop postoperative renal impairment. Four selected control patients were excluded because of inadequate case records. Ninety-three parameters were recorded on the 38 patients with renal impairment and on the 196 control patients. The parameters recorded are listed below and included basic patient data, details of the previous medical history, admission history and examination findings, details of the pre-operative course, details of radiological, haematological and biochemical investigations, and details of the operation and of the postoperative course.

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Details of data recorded

The following data were recorded.

Patient data: age, sex, race, smoking habits and alcohol intake.

Previous medical problems: cardiac disease, pulmonary disease, renal disease, diabetes mellitus, hypertension, jaundice, gastrointestinal bleeding, pancreatitis, encephalopathy, biliary surgery, renal dialysis and steroid therapy.

Admission details: weight loss (percentage within previous 6 months), recent febrile episodes, presence of jaundice, ascites, abnormal cardiac examination findings, abdominal tenderness or peritonism, a palpable abdominal mass, an infected abdominal wound, an external abdominal fistula or biliary drain, and clinical evidence of sepsis (temperature > 38°C).

Pre-operative data: pyrexia (> 38°C), external percutaneous biliary drainage (days), parenteral nutrition (days), bile infection, other infection and aminoglycoside therapy (days).

Radiological investigations: percutaneous transhepatic cholangiography, visceral angiography, CT scanning and ERCP, complications of radiological investigation and evidence of portal vein or hepatic arterial involvement.

Laboratory data: admission (within 2 days of admission to hospital) and pre-operative (result before surgery) values for serum bilirubin, alkaline phosphatase, aspartate transaminase, albumin, creatinine, urea, amylase, haemoglobin, white cell count, platelet count, prothrombin time, and partial thromboplastin time (kaolin).

Operative data: perioperative mannitol infusion, liver or pancreatic resection, cirrhosis, lobar liver atrophy, the presence of intra-abdominal sepsis, operative bile culture, the occurrence of perioperative hypotension (systolic blood pressure < 80 mmHg for > 10 min), the duration of general anaesthesia (min), the volume of blood transfused during surgery (units), the volume of fresh frozen plasma or plasma protein fraction transfused (ml) and the volume of albumin or plasma substitute transfused (ml).

Postoperative data: reoperation for sepsis, reoperation for bleeding, any abdominal reoperation, postoperative bacteraemia (positive blood culture), postoperative sepsis (pyrexia > 38°C and white cell count $11\,000 \times 10^9$/l more than 72 h postoperatively), postoperative bleeding (requiring at least 2 units of blood transfused, gastrointestinal or intra-abdominal), urine infection, the presence of an intra-abdominal abscess or infected fluid collection, postoperative pancreatitis, pulmonary complications, cardiac complications, pulmonary embolus, abdominal fistula, wound infection, liver failure (no postoperative improvement, or a continued deterioration in postoperative liver function tests), and death (within 30 days of initial surgery).

All these items were recorded as a numerical value, positive/negative, present/absent, or normal/abnormal unless otherwise stated.

Statistical analysis

The two groups of patients were initially compared using standard univariate statistical tests (Fisher, χ^2, Mann–Whitney *U* and *t* tests as appropriate) to identify those data significantly associated with the development of postoperative renal impairment. Stepwise logistic regression analysis was then performed on these data using the BMDP Statistical Package[11].

Postoperative course in patients with renal impairment

In addition, an analysis of the postoperative course and of any specific treatment required for renal failure was made in the 38 patients who developed renal impairment. The timing of renal impairment (as defined above) in relation to surgery and death (if appropriate) was recorded. The requirement for ventilatory support before death, the number and nature of postoperative complications, the number of reoperations (with indications), and the duration of oliguria (< 500 ml urine/24 h) were also noted. The number of organ system failures (i.e. systems requiring some specific supportive therapy, including the respiratory, cardiovascular, central nervous, liver and coagulation systems) in addition to renal impairment was estimated from case records. The probable causes of renal impairment in these patients were noted when the contemporaneous opinion of the consulting renal physicians was found. Fisher, χ^2 and Mann–Whitney *U* tests were used for analysing differences within this group.

Results

The patient groups

One patient with primary sclerosing cholangitis developed acute renal failure requiring dialysis before surgery and was the only patient undergoing biliary tract surgery who was excluded from further analysis. There was no significant difference in diagnosis (*Table 1*) or in operative procedure between the two groups of patients. Major organ resections (pancreatic head or liver) were performed in 4 patients who developed renal impairment and in 26 who did not. Seventy per cent of all patients had a serum bilirubin > 50 μmol/l pre-operatively, 32 in the renal impairment group and 131 other patients. Overall 61 per cent of the patients studied had undergone previous biliary surgery.

Seventy-three patients had pre-operative percutaneous transhepatic biliary drainage. This group had a higher 30 day mortality (27 *versus* 16 per cent, $P = 0{\cdot}05$) and admission serum bilirubin (mean 255 μmol/l *versus* 175 μmol/l, $P < 0{\cdot}05$) compared with non-drained patients, a similar incidence of renal impairment (14 *versus* 17 per cent) and postoperative sepsis (25 per cent for both groups), and a lower pre-operative serum bilirubin (132 μmol/l *versus* 204 μmol/l, $P < 0{\cdot}01$).

Factors associated with renal impairment

Twenty-one of the parameters examined were significantly associated with postoperative renal impairment using univariate analysis (*Table 2*). There was no significant association between renal impairment and any of the other factors examined; in particular there was no association with perioperative hypotension, pre-operative evidence of infection, pre-operative serum creatinine, or malignancy. Many of the parameters listed in *Table 2* were closely associated with each other and, after stepwise logistic regression analysis of the significant univariate associations (except postoperative death), only three retained a significant effect on the fit of the regression equation: postoperative sepsis, pre-operative serum bilirubin and pre-operative serum urea (*Table 3*). Using these three parameters alone 21 (55 per cent) of the patients with renal impairment and 179 (91 per cent) of the control patients were correctly classified. When pre-operative factors alone were analysed, they proved less powerful in separating the two groups: the pre-operative parameters which retained a significant effect were pre-operative serum bilirubin and abdominal tenderness on admission (*Table 3*). Pre-operative serum urea no longer carried a significant effect.

Treatment of renal impairment

Renal impairment developed at a median of 4 days after initial surgery (range 1–54). Only 16 patients developed oliguria. Patients with renal impairment fell into three categories (*Table 4*): those who survived without therapy for renal impairment, those who required therapy for renal failure, and those who developed renal impairment as a terminal event in association with multiple organ system failures when specific therapy was either not necessary or felt to be contra-indicated. Dialysis or haemofiltration was used in nine patients. Four had

Table 1 *Diagnoses of patients with and without renal impairment after biliary tract surgery*

Diagnosis	Patients with renal impairment (percentage of total)	Patients without renal impairment (percentage of total)
Cholangiocarcinoma	16 (42)	64 (32)
Benign bile duct stricture	8 (21)	57 (29)
Pancreatic carcinoma	5 (13)	23 (11·5)
Choledocholithiasis	2 (5)	19 (10)
Periampullary tumour	2 (5)	10 (5)
Gallbladder carcinoma	4 (11)	7 (4)
Papillary stenosis	—	3 (1·5)
Choledochal cyst	—	3 (1·5)
Biliary fistula	—	3 (1·5)
Other lesions	1 (3)	7 (4)
Total	38 (100)	196 (100)

Table 2 *Factors significantly associated with the development of postoperative renal impairment*

Factor	Patients with renal impairment	Patients without renal impairment	*P*
Abdominal reoperation	17/38	18/196	<0·0001
Pre-operative serum bilirubin (μmol/l)*	221 (8–687)	84·5 (3–775)	<0·0001
Postoperative bacteraemia	14/38	21/196	<0·0001
Reoperation for sepsis	12/38	12/196	<0·0001
Death within 30 days of surgery	25/38	21/196	<0·0001
Postoperative sepsis	28/38	31/196	<0·0001
Postoperative pulmonary complication	26/38	60/196	<0·0005
Postoperative bleeding	13/38	20/196	<0·0005
Pre-operative serum urea (mmol/l)*	6·25 (2·9–41·8)	4·4 (1·3–33·8)	<0·001
Admission serum bilirubin (μmol/l)*	260·5 (8–675)	133 (3–745)	<0·005
Pre-operative serum albumin (g/l)*	32 (20–45)	36 (23–49)	<0·005
Admission prothrombin time (s)*	14 (10–31)	13 (10–66)	<0·005
PPF/FFP transfused during surgery (ml)*	400 (0–1800)	0 (0–400)	<0·005
Postoperative liver failure	6/38	3/195	<0·005
Age (years)*	62·5 (18–74)	53 (15–85)	<0·01
Postoperative abdominal abscess	9/38	13/196	<0·01
Previous cardiac disease	9/38	19/196	<0·05
Abdominal tenderness on admission	6/38	9/196	<0·05
Perioperative mannitol infusion	28/37	86/167	<0·05
Admission serum albumin (g/l)*	34 (20–44)	37 (23–52)	<0·05
No previous biliary surgery	21/38	71/196	<0·05

* Median values (range)

Table 3 *Factors significantly associated with renal impairment after stepwise logistic regression analysis*

Factor	Improvement in χ^2	*P*
All factors		
Postoperative sepsis	48·6	<0·0005
Pre-operative serum bilirubin	12·6	<0·0005
Pre-operative serum urea	4·0	<0·05
Pre-operative factors only		
Pre-operative serum bilirubin	16·3	<0·0005
Abdominal tenderness	8·1	<0·005

Table 4 *Treatment given for postoperative renal impairment*

		Treatment			
Patient group	*n*	None	Fluid restriction	Dialysis/ haemofiltration	Other*
Survivors	10	9	—	1	—
Hospital deaths	28	9†	7	8	4
All cases	38	18	7	9	4

* Dextrose and insulin infusions (two patients, with fluid restriction in one), dopamine infusion in one patient, and additional intravenous fluids in another patient with polyuric renal failure

† Specific therapy not required or considered inappropriate because of associated problems

haemodialysis, three had peritoneal dialysis, one had haemofiltration and the final patient had both haemodialysis and haemofiltration. The median duration of treatment of these nine cases was 4 days (range 1–27).

Associations with renal impairment

Patients with renal impairment had a median of two additional major postoperative complications (range 0–4). These complications comprised abdominal sepsis (or cholangitis) in 26 patients, infective respiratory complications in 18 patients, postoperative haemorrhage in 13 patients (gastrointestinal in 7, intra-abdominal in 4, both in 2), pancreatic, biliary or intestinal fistulae in 8 patients, cardiovascular complications in 7 patients, hepatic failure in 6 patients, and other complications in 4 patients. Infection (intra-abdominal or pulmonary) was the most common postoperative complication and was significantly associated with reoperation ($P<0·05$) and with the development of one or more organ system failure(s) in addition to renal impairment ($P<0·05$). Seven patients were ventilated at the time of death. Of the 38 patients who developed postoperative renal impairment, 17 underwent a total of 24 reoperations for suspected intra-abdominal sepsis (14 operations), haemorrhage (8 operations) or fistula (2 operations). The median period between initial surgery and first reoperation was 10 days (range 0–32), and the first reoperation was done before the development of renal impairment in 10 of these patients, on the same day in three, and after renal impairment in only four (the median interval from first reoperation to renal impairment was one day, range −16 to 18).

Causes of renal impairment

The major cause or causes of renal impairment which were considered important by the consulting renal physicians in these 38 patients were intra-abdominal or respiratory sepsis (29 patients), haemorrhage (8 patients), inadequate hydration (2 patients), and aminoglycoside therapy (1 patient). The following additional factors were also considered to have contributed to some extent to the development of renal impairment: aminoglycoside therapy (13 patients), hepatic failure (5 patients), cardiac failure (5 patients), sepsis (4 patients), inadequate hydration (3 patients), haemorrhage (2 patients) and partial ureteric obstruction (1 patient). In four patients no cause was recorded. Three of these four patients survived and required no therapy for renal impairment; the other died of inoperable malignancy without successful biliary decompression or treatment for renal impairment.

Mortality associated with renal impairment

Twenty-eight (74 per cent) of the patients with postoperative renal impairment died without leaving hospital. The median interval between initial surgery and death was 15 days (range 2–55), and this group had a median interval of 5 days postoperatively before renal impairment developed (range

1–54). Sixteen of the twenty-eight deaths (57 per cent) occurred within 7 days of the development of renal impairment. The patients who died with renal impairment had a median two other organ system failures before death (range 0–4). Only one patient died without another organ system failure before death, a patient with known ischaemic heart disease, who had a cardiac arrest during haemodialysis. No other patient died directly as a result of renal impairment or its treatment.

The patients with renal impairment who died had a higher serum bilirubin ($P < 0{\cdot}05$) and serum creatinine ($P < 0{\cdot}05$), and a lower serum albumin ($P < 0{\cdot}005$) and were more likely to have malignant disease ($P < 0{\cdot}01$) and to have had pre-operative percutaneous biliary drainage ($P < 0{\cdot}05$) than the patients with renal impairment who survived. There was no significant difference in age or pre-operative serum creatinine. The patients who died with renal impairment also had a significantly higher number of organ system failures ($P < 0{\cdot}001$), and more severe renal impairment (a larger maximum rise in serum creatinine, $P < 0{\cdot}005$, and a higher incidence of oliguria, $P < 0{\cdot}005$). Twenty-three of the twenty-eight patients with renal impairment *and* postoperative sepsis died compared with only six of the thirty-one patients with postoperative sepsis in the absence of renal impairment.

Discussion

The patients in this study were a selected group treated in a specialist hepatobiliary unit. Many of these patients were at high risk, the majority had undergone previous biliary surgery and 31 per cent had pre-operative percutaneous biliary drainage. Thus they are atypical of biliary tract surgery in general. However, this large group of patients, 70 per cent of whom were jaundiced pre-operatively, provided a good opportunity to analyse in detail the factors associated with renal impairment following biliary tract surgery, and it is likely that these factors will also be relevant to less selected groups of patients. The incidence of postoperative renal impairment in this series is similar to that found by others[4–9].

Multivariate stepwise logistic regression analysis identified two major 'independent' factors associated with postoperative renal impairment: postoperative sepsis and an elevated pre-operative serum bilirubin. This suggests that postoperative infection is the major factor associated with renal impairment in patients with obstructive jaundice.

Examination of the postoperative course in patients who developed renal impairment clearly shows that renal impairment following biliary tract surgery was almost invariably associated with other major postoperative complications, in particular intra-abdominal and respiratory infection, liver failure and postoperative bleeding. The timing of renal impairment in relation to surgery suggests that renal impairment was usually not a direct consequence of initial surgery itself, but frequently related to the subsequent development of postoperative problems. This suggestion is supported by the finding that reoperation was undertaken for haemorrhage or suspected sepsis before or on the same day as the development of renal impairment in over a third of cases. These conclusions are in agreement with the studies of Kornhall[12], Kennedy *et al.*[13] and Marshall[14].

The mortality of patients treated on renal units for renal failure after biliary tract surgery reported by Kornhall[12] and Kennedy *et al.*[13] was 79 per cent and 69 per cent respectively, and is comparable with our own results. The frequency and severity of complications associated with postoperative renal impairment in the current series is emphasized by the apparent ineffectiveness of specific treatment for renal failure in influencing the final outcome of the patients.

Sorensen *et al.*[15] advocated an aggressive surgical approach in patients who developed renal failure in biliary tract disease, or after biliary tract surgery, because they thought that renal failure was usually associated with cholangitis or surgical complications. Despite the use of such an aggressive policy in the management of patients in this study, the mortality associated with renal impairment remained high.

The relatively high incidence (58 per cent) of non-oliguric acute renal impairment seen in this study is similar to that reported by Anderson *et al.*[16], and there is an increasing awareness of this condition. The development of oliguria appears to carry a worse prognosis.

The mortality considered to be primarily due to renal failure after surgery for obstructive jaundice has been reported to range from 4 to 13 per cent[1–6]. The findings of this study suggest that other complications of biliary tract surgery usually underlie the development of renal impairment, which itself is an accompaniment to rather than the major cause of death. Certainly the mortality of acute tubular necrosis complicating other conditions is much lower than that seen after abdominal surgery[13], and this suggests that the mortality directly attributable to renal failure and its therapy is low. Similar conclusions were drawn by Mentzer *et al.*[17] who have studied acute tubular necrosis following renal transplantation.

Acute renal failure itself might contribute to an increased incidence and severity of other postoperative complications, for example by affecting host defence responses to sepsis. The mortality of patients with postoperative renal impairment and sepsis in this study was higher than that of patients with sepsis alone. Thus, renal impairment may be an important indirect cause of mortality in patients with multiple organ failure, or it may simply reflect the severity of their postoperative complications, particularly sepsis.

There is clear evidence from the previous studies of others[1,2,9] that postoperative renal failure is commoner in patients with obstructive jaundice than in non-jaundiced patients. However, few groups of surgical patients have postoperative morbidity and mortality rates comparable to that of obstructive jaundice. Thus, the high incidence of renal failure in these patients might be largely consequent on this high complication rate, rather than on an increased susceptibility to renal injury *per se*. The 'independent' significance of pre-operative serum bilirubin as a factor strongly associated with the development of renal impairment in this study, even when any association with postoperative sepsis and other complications had been taken into account, provides clinical evidence for an increased incidence of renal injury directly related to obstructive jaundice itself. The pathophysiological mechanism of this increased renal susceptibility to injury in obstructive jaundice remains uncertain, although a number of possible factors have been suggested including hypovolaemia[1], conjugated bilirubin[18], bile salts[19,20], renovascular fibrin deposition[21–23], endotoxaemia[24–26], and alterations in systemic and renal haemodynamics[27].

Clearly, continued close attention to adequate pre-operative hydration and perioperative renal function is necessary in all patients undergoing biliary tract surgery. However, the findings of this study suggest that the prevention of postoperative renal failure in patients with obstructive jaundice, whilst obviously desirable, might not by itself substantially reduce mortality. A reappraisal of surgical attitudes to renal failure in these patients may be necessary so that attention might be concentrated on the prevention of other major postoperative complications, particularly sepsis, the reduction of which should be accompanied by a concomitant reduction in the incidence of renal impairment.

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Biliary lithiasis in the over seventy-five age group: a new therapeutic strategy

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Sixty-four gallstone patients aged 75 or more (mean age 83 ± 5·1 years) were divided prospectively into two groups. They were mostly high-risk patients (average number of major risk factors, 2·2 ± 0·9). Thirty-three showed one or several signs of lithiasis of the common bile duct and were treated with endoscopic sphincterotomy (ES) (31 successful cases, two technical problems) followed by early cholecystectomy (33 cases). Choledocholithiasis was present in 26 cases and stones were extracted in 25 cases. Two patients (6 per cent) died. ES caused no complications. Thirty-one other patients showed no sign of choledocholithiasis and were treated by cholecystectomy with operative cholangiography. Choledocholithiasis was found in two of these patients and treated by extraction and external drainage. Five of these patients (16 per cent) died. In 30 cases acute cholecystitis was found at operation, 15 in each group. ES is therefore an efficient procedure in high-risk patients, which facilitates operation, especially in cases of acute cholecystitis, and it is recommended in all cases of complicated biliary lithiasis. Early cholecystectomy is justified for these patients by the high frequency of associated acute cholecystitis.

Keywords: Cholelithiasis, sphincterotomy, endoscopy

Surgical treatment of biliary lithiasis exposes patients over 75 to a high mortality rate, especially when the problem is complicated by infection or the presence of stones in the common bile duct (CBD)[1,2]. This led us to approach the problem in patients thought to have stones in the CBD by endoscopic papillotomy followed by surgery limited to the gallbladder.

Patients and methods

In the 2 year period June 1984–May 1986, 64 patients aged 75 and over (average age: 83 ± 5·1 years) underwent operation for biliary lithiasis. They were divided into two groups, according to the presence of one or more of the five following criteria which may be associated with CBD lithiasis: common bile duct >8 mm on ultrasonography or >10 mm on cholangiography; serum alkaline phosphatase >200 units/l (normal ⩽96 units/l); serum amylase >80 units/l (normal ⩽40 units/l); present or past history of jaundice; serum bilirubin >40 μmol/l (normal ⩽20 μmol/l.

The 33 patients in group I, suspected of having CBD lithiasis, were treated by endoscopic retrograde cholangiography (ERCP) with endoscopic sphincterotomy (ES) followed by early cholecystectomy (within 1–3 days) without operative exploration of the CBD. All patients having had ES proceeded to operation.

The 31 patients in group II, not fulfilling any of the above criteria, had cholecystectomy with operative cholangiography.

The results were considered in relation to the following: age; whether the patient had been admitted from home or a long stay unit; number of operative risk factors i.e. general (bed sore, bedridden); vascular (myocardial infarction <6 months, cardiac failure); pulmonary (preoperative respiratory disease with $P_{a,O_2} \leqslant 60$ mmHg); infection with positive blood cultures; neurological (senile dementia, past history of stroke).

The criteria used for assessment of results were: operative mortality (within 30 days of surgery); morbidity; the presence of choledocholithiasis and the presence of acute cholecystitis. The diagnosis of acute cholecystitis was based on macroscopic operative examination, with pathological confirmation (gangrenous, perforation, empyema). Statistical analysis was performed using the χ^2 test.

Results

All group I patients but one underwent ERCP. In this patient it was technically impossible to catheterize the papilla because of the presence of duodenal diverticula. At operation there were many stones in the common duct and after removing the obstruction choledochoduodenostomy was carried out.

All the other patients in group I except one had an ES. In this patient, ERCP showed a small calibre CBD without calculi so ES was abandoned. Ten further patients also had a negative ERCP but ES retrieved small stones in four of the patients and frank pus in one.

Table 1 shows the comparability of the two groups.

Mortality

The overall operative mortality was 11 per cent (seven cases); two patients dying in group I (6 per cent) and 5 cases in group II (16 per cent) (n.s.).

The two deaths in group I were due, respectively, to respiratory distress which developed on the 17th day after the operation in the patient who had not undergone a sphincterotomy, and to circulatory failure on the first day following a peroperative myocardial infarction.

The five deaths in group II were due to: pulmonary embolism despite heparin prophylaxis (two patients); massive stroke (one patient), acute pyelonephritis with septicaemia (one patient) and in the last patient death occurred 6 weeks after cholecystectomy carried out for acute calculous cholecystitis. Cholecystitis in this patient was a complication of acute pancreatic necrosis, and was due to the spreading of the necrosis.

Morbidity

No complications of ES were observed; in particular there was no instance of haemorrhage from the sphincterotomy site and no acute pancreatitis.

No surgical complications occurred in either group.

Lithiasis of the CBD

In group I, choledocholithiasis was present in 26 patients. The CBD was cleared of stones in 25 patients whereas in one the stone was encrusted in the hepatic duct and associated with a biliary fistula. In one patient the ES drained frank pus, bringing

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Table 1 *Patient details*

	Group I	Group II	*P*
n	33	31	
Sex	3 M/30 F	6 M/25 F	n.s.
Mean age (±s.d.)	83·5 (±5·4)	82·4 (±4·7)	n.s.
Admitted from home	10	6	
Admitted from long stay unit	23	25	n.s.
Risk factors/patient	2·27 (±0·86)	2·25 (±0·98)	n.s.

the number of productive ESs to 26 (79 per cent of all patients).

In group II, choledocholithiasis was found on operative cholangiography in two cases, neither of whom died. The obstruction was removed after choledochotomy, and external drainage by T-tube was establsihed. Residual stones were not observed.

The sensitivity and specificity of the criteria used to allocate patients to pre-operative ERCP were therefore 93 and 81 per cent respectively.

Acute cholecystitis

Acute cholecystitis was present in 30 patients, 4 of whom died (13 per cent).

In group I, acute cholecystitis was present in 15 patients, none of whom died. Only 3 had a pre-operative fever, but 12 had one of the following: a recent febrile episode; leucocytosis $>10\,000/\text{mm}^3$; right upper quadrant tenderness or gallbladder wall >3 mm on ultrasonography. Thirteen patients had choledocholithiasis.

In group II, 15 patients had acute cholecystitis, 4 of whom died.

Discussion

The reported mortality rate, which is the principal criterion in judging biliary duct surgery in elderly patients varies from 1 per cent[3], to 30·5 per cent[1]. This rate is increased by three main factors: the number of operational risk factors, the presence of infection, and the presence of choledocholithiasis when it leads to choledochotomy[2,4]. These complicating factors are more common in the elderly[5], the incidence of acute cholecystitis sometimes reaching 47 per cent[2], while stones may be present in the CBD in 46 per cent of the patients operated upon with gallstones[3]. These observations and the high mortality rate in our previous series[2] led us to change our therapeutic strategy and to introduce pre-operative endoscopic sphincterotomy in elderly patients with suspected choledocholithiasis.

It is well established that ES has an incidence of complications which is <10 per cent. These complications, notably haemorrhage and acute pancreatitis, are rarely serious, and have a mortality rate of <2 per cent[6–12]. Subsequent complications, such as cholangitis, stenosis and recurrent lithiasis are also exceptional[10,13–15]. This has allowed the performance of ES in high risk patients with a gallbladder *in situ*[16]. In fact in our series of 31 ES, no complication was observed, and no deaths were attributed to this technique.

The advantages of ES before the cholecystectomy in a patient showing signs of choledocholithiasis, are reduction in the duration of operation, its simplification especially when there are inflammatory phenomena, avoidance of peroperative cholangiography, and especially avoidance of the need to open the CBD and drain it externally or internally. These advantages have been decisive in the aged patients in this series, most of whom were high-risk: mortality was 6 per cent whereas it had been 21 per cent in our previous series of patients having choledochotomy[2]. Furthermore, this new therapeutic strategy reduced overall mortality from 23 to 11 per cent[2]. It should be stressed that the patients of the previous series were comparable in terms of mean age (83·2 ± 5·2), origin (36/144 from home) and risk factor score (2·21 ± 0·9).

Acute cholecystitis after ES is rare with a reported incidence of about 6 per cent[7,8,10,17], justifying for some the lack of need to perform cholecystectomy. Furthermore, immediate acute cholecystitis as a complication of ES also seems to be rare: Neoptolemos *et al.*[16] only mention 2 cases in 97 patients having previously had an ES. In our series on the other hand, the rate of acute cholecystitis was high. This rate was not related to the ES for it was the same with and without ES, and in our previous series (about 50 per cent)[2]. This high prevalence of acute cholecystitis justifies cholecystectomy after ES in our patients.

The predictive value of the criteria for pre-operative endoscopic treatment also proved insufficient, with two false negatives (surgical removal of stones), and seven false positives (no stones in the CBD). This now leads us to perform pre-operative ES at the slightest suspicion of complicated biliary lithiasis in aged high-risk patients, given its low mortality and morbidity. However for younger patients, or older but lower risk patients, this approach cannot for the moment be adopted as a routine practice in the absence of any demonstrable superiority over surgery alone.

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Effect of vagal denervation on canine gallbladder motility

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There is an increased incidence of gallstones after truncal vagotomy but the mechanism is unknown. Our aim was to study the early effects of vagotomy on fasting and postprandial gallbladder motility. A chronic model was constructed in 10 dogs to correlate gallbladder motility and emptying with interdigestive and postprandial duodenal motility both before and after selective hepatobiliary vagotomy (five dogs) and truncal vagotomy (5 dogs). During each study recordings were made for one complete interdigestive motor complex (IDMC) and for 90 min after a standard meal of (a) gallbladder and duodenal motility, (b) gallbladder emptying (by a dual radioisotope marker technique) and (c) duodenal output of bilirubin. In control studies the gallbladder contracted at the start of phase II of the interdigestive motor complex and ejected 20–25 per cent of its contents into the duodenum; after meals the gallbladder contracted within 5 min and emptied almost 80 per cent of its contents within 90 min. After both selective hepatobiliary vagotomy and also truncal vagotomy there was no significant difference in the pattern of contraction or emptying of the gallbladder either during fasting or postprandially. We conclude that gallbladder motility and emptying are entirely normal in the early period after vagal denervation.

Keywords: Vagotomy, gallbladder, motility, emptying

Several clinical studies have documented an increased incidence of gallstones following truncal vagotomy for peptic ulcer disease[1–5]. The magnitude of this problem is not clear, but it appears that patients who have had a truncal vagotomy have a 4–5 times greater risk of developing gallstones compared with normal individuals[4,5]. The mechanism of this gallstone development is uncertain but the development of biliary stasis has often been cited as the most important factor since previous radiological studies have shown that truncal vagotomy is followed by the gradual development of a dilated and hypotonic gallbladder[6,7]. However, it is not clear why vagotomy should cause gallbladder stasis since the primary mechanism controlling gallbladder function is hormonal rather than neural[8–10], and indeed the precise role of the vagal supply to the gallbladder has not been defined.

This study was undertaken to examine the contribution of the vagus nerves to gallbladder motor function by determining the effect of vagotomy on fasting and postprandial gallbladder motility and emptying. The study was performed utilizing a dog model so that motor events in the gallbladder before and after different types of vagotomy could be correlated with known interdigestive and postprandial duodenal motor events and so that gallbladder emptying could be precisely quantitated. The studies were performed as soon as possible after vagotomy so that the primary effect of vagal denervation on gallbladder motility could be determined before any secondary effects, e.g. change in gallbladder wall compliance or change in sphincter of Oddi resistance, could exert an appreciable effect.

Methods

Animal model

Ten male dogs, each weighing 20–25 kg, were used to prepare a chronic dog model. A midline abdominal incision was made under general anaesthesia. Two polyethylene catheters (ID = 1·14 mm) were placed in the gallbladder through a small stab incision in the fundus. These were held in place by a 1·5 cm plastic disc which was sutured to the serosa of the gallbladder wall. One of these catheters was used to monitor pressure inside the gallbladder and the other was for introduction of a radioisotope marker. Three polyethylene catheters were inserted in the duodenum through a small stab incision 1 cm distal to the pylorus. These were also held in place by a plastic disc which was sutured to the duodenal wall. The first catheter (ID = 1·14 mm) had its tip 1 cm distal to the stab site and was used to perfuse the duodenum with radioisotope marker; the second catheter (ID = 1·14 mm) had its tip at the level of the pancreatic duct orifice and was used to monitor intraduodenal pressure; the third catheter (ID = 3 mm) had its tip in the most distal part of the duodenum and was used to collect duodenal contents for analysis (*Figure 1*). The gallbladder catheters and the duodenal catheters were brought out through two separate metal ports which were embedded in the anterior abdominal wall and these were plugged with wax when studies were not being performed. The dogs were allowed to recover for at least 2 weeks before definitive studies were performed. During this period the catheters were gently flushed with sterile water twice weekly to maintain patency, and intermittent motility recordings were made to monitor the return of interdigestive motor activity.

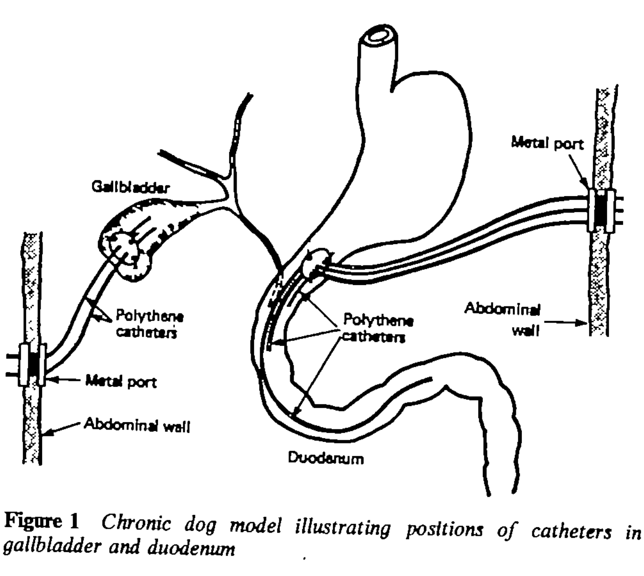

Figure 1 *Chronic dog model illustrating positions of catheters in gallbladder and duodenum*

Each dog had a control study (see below) to document its normal pattern of gallbladder motility and empyting and was then returned to the operating room for either a hepatobiliary vagotomy (five dogs) or a truncal vagotomy (five dogs). For the hepatobiliary vagotomies the abdomen was opened through a left subcostal incision. The hepatobiliary branches of the vagal trunks were identified below the diaphragm and were divided. Great care was taken to identify and preserve the main vagal trunks and the vagal supply to the stomach. In order to ensure complete hepatobiliary denervation the lesser omentum was divided close to the liver from the lower oesophagus to the pylorus. For the truncal vagotomies a left posterolateral thoracotomy was performed through the seventh intercostal space. The main vagal trunks and any small vagal fibres were identified on the lower oesophagus and were completely divided. Gastric drainage procedures were not performed in order to avoid a disturbance of gallbladder contraction due to alteration of gastric emptying patterns. The 10 dogs had a further postoperative recovery period of 2 weeks before postvagotomy studies were performed.

Study design

Studies were performed after an 18 h fasting period. The dogs stood upright in a Pavlov sling and did not receive any sedation. The duodenal perfusion catheter was perfused with a solution of [^{3}H]PEG (polyethylene glycol) commencing at least 1 h before studies began. This solution contained 30 μCi [^{3}H]PEG in 1 litre of water and was kept at 37°C durıng constant perfusion at 3·5 ml/min. The pressure-recording catheters in the gallbladder and duodenum were water filled but were not perfused and pressure changes were transmitted through strain-gauge transducers to a pen-writing multichannel recorder. The distal duodenal catheter was left open for free drainage and collection of duodenal contents. The non-perfused technique of pressure recording was chosen to avoid causing changes in gallbladder volume which would alter its motility or emptying patterns.

Each study commenced at the beginning of phase I of the interdigestive motor complex (IDMC) as observed in the duodenal pressure-recording catheter. At that time 0·5 μCi [^{14}C]PEG (0·5 ml) was slowly instilled into the gallbladder and its subsequent output into the duodenum was used to quantitate (see below) gallbladder emptying. (Phase I of the IDMC is the resting phase between two successive migrating motor complexes (MMCs) during which there is virtually no contractile activity in the duodenum—this phase usually lasts 60–80 min; phase II is the phase of irregular sporadic motor activity which signals the approach of MMCs—it usually lasts 20–30 min; phase III is the phase of regular large amplitude contractions which reflect the passage of an MMC and it usually lasts 10–15 min.) Pooled duodenal collection samples were removed in ice for analysis at 15 min intervals during one complete IDMC. The dogs were then fed a standard meal of minced dog meat and full-cream milk and the studies continued for a further 1½ h. Throughout each study gallbladder and duodenal pressures were continually monitored and the colour of the duodenal drainage fluid was constantly observed. The appearance of bile in the duodenal effluent was noted and marked on to the duodenal motor activity recording. The collected duodenal samples were analysed for ^{3}H and ^{14}C by liquid scintillation counting and for bilirubin content by colorimetry in a Cobas B10 centrifugal analyser.

Data analysis

The following calculations were performed for each 15 min duodenal sample to arrive at a quantitation of gallbladder emptying (see below for explanation of symbols):

1. Duodenal volume flow, $\mathrm{DVF} = \dfrac{[[^3\mathrm{H}]\mathrm{PEG}]_i \times V_i}{[[^3\mathrm{H}]\mathrm{PEG}]_o}$
2. Duodenal output of GB marker $= \mathrm{DVF} \times [[^{14}\mathrm{C}]\mathrm{PEG}]_o$
3. Duodenal output of bilirubin $= \mathrm{DVF} \times [\mathrm{Bili}]_o$

$[[^3\mathrm{H}]\mathrm{PEG}]_i$ = concentration of ^{3}H in duodenal perfusate; $[[^3\mathrm{H}]\mathrm{PEG}]_o$ = concentration of ^{3}H in duodenal collections; V_i = volume of duodenal perfusate per 15 min (i.e. 15 × 3·5 ml); $[[^{14}\mathrm{C}]\mathrm{PEG}]_o$ = concentration of ^{14}C in duodenal collections; $[\mathrm{Bili}]_o$ = concentration of bilirubin in duodenal collections.

Gallbladder emptying during any particular period was then calculated by expressing duodenal output of the gallbladder marker for that period as a percentage of gallbladder content of the marker at that time. The outputs of bilirubin and gallbladder marker and the percentage emptying of the gallbladder for different phases during the interdigestive and postprandial periods were compared for control and postvagotomy studies using Student's *t* test for paired data.

Results

Following the initial laparotomy a normal eating pattern was usually resumed within 2–3 days. However, the interdigestive motility pattern in the duodenum generally took 5–7 days to return completely to normal. After hepatobiliary vagotomy there was a similar delay in the return of normal patterns of interdigestive motility. However, after truncal vagotomy the return of normal patterns was considerably delayed. In a separate pilot study motor complexes were often seen as early as 5 days postoperatively but were not migratory. However, return of MMCs always occurred by the 10th–12th postoperative day. Most dogs could tolerate only fluids for 6–10 days after surgery but several dogs in the pilot study had difficulty with solids for 3–4 weeks. For this reason all dogs in the present study were given semi-solid meals of minced meat with milk during both control and postvagotomy studies and this was easily tolerated after the eighth day post truncal vagotomy. The return of completely normal interdigestive motor activity was usually delayed for 10–12 days following truncal vagotomy.

Interdigestive period

During phase I and phase III of each IDMC the gallbladder intraluminal pressures remained fairly constant and were similar in control (10 ± 1 cmH_2O), post hepatobiliary vagotomy (9 ± 2 cmH_2O) and post truncal vagotomy (10 ± 2 cmH_2O) studies. However, almost immediately after the commencement of phase II activity in the duodenum, the gallbladder pressure rose to 19 ± 3 cmH_2O, 19 ± 2 cmH_2O and 20 ± 2 cmH_2O respectively in the three groups as shown in *Figure 2*. These pressure rises were transient (generally less than 3 min duration) and the sharp return of pressures to baseline values was followed by the appearance of bile in the duodenal contents (*Figure 2*, asterisks). The duodenal effluent remained clear during phase I and most of phase III of the IDMC in all three study groups but the duodenal contents became bile stained immediately after the transient pressure elevations at the start of phase II (*Figure 2*, asterisks). Bile output ceased either just before or immediately after the onset of phase III contractions. During phase II the gallbladder ejected 21 ± 2 per cent (controls), 21 ± 3 per cent (post hepatobiliary vagotomy) and 22 ± 2 per cent of its contents of [^{14}C]PEG and the duodenal output of bilirubin was 11 ± 1 μmol, 10 ± 1 μmol and 9 ± 2 μmol respectively (*Figure 3*). None of these differences were statistically significant.

Postprandial period

Gallbladder pressures rose to 23 ± 2 cmH_2O (controls), 21 ± 2 cmH_2O (post hepatobiliary vagotomy) and 22 ± 3 cmH_2O (truncal vagotomy) within 4 ± 1 min, 5 ± 1 min and 4 ± 2 min of ingesting the standard meal (*Figure 4*). These pressure rises lasted 3 ± 1 min and then returned to baseline levels. There was no significant difference between the three groups in regard to postprandial gallbladder motility. In all three study groups the duodenal contents became bile stained immediately following the rises in gallbladder pressure (*Figure 4*, asterisks) and remained bile stained throughout the following 90 min. Duodenal output of gallbladder marker during the first 30 min after eating was 37 ± 2 per cent, 36 ± 2 per cent and 38 ± 1 per cent of gallbladder contents for the control, post hepatobiliary vagotomy and post truncal vagotomy groups respectively. By 90 min the gallbladder had ejected 77 ± 1 per cent, 76 ± 1 per cent and 78 ± 1 per cent of its contents (*Figure 5*). Duodenal output of bilirubin was maximal during the first 30 min and by 90 min the cumulative duodenal output of bilirubin in the three groups was, respectively, 84 ± 1 μmol, 86 ± 2 μmol and 85 ± 1 μmol (*Figure 5*). These differences in gallbladder emptying and duodenal output of bilirubin were not significant.

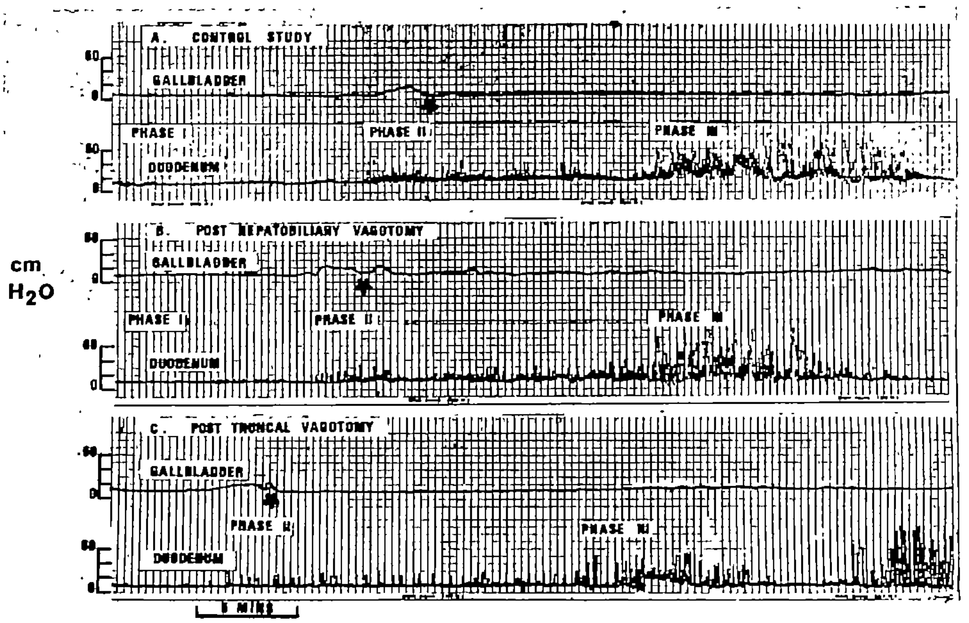

Figure 2 *Simultaneous recording of interdigestive motor complex in duodenum and interdigestive pressure changes in gallbladder. Asterisk marks time of appearance of bile in duodenal contents*

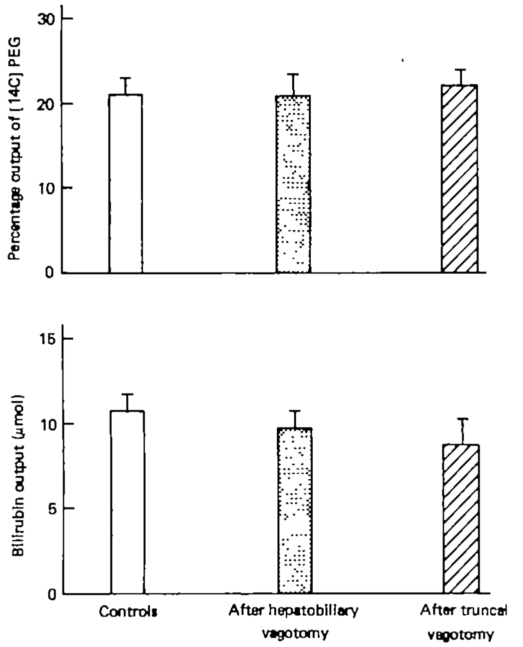

Figure 3 **a**, *Gallbladder emptying (percentage output of [^{14}C]PEG) and* **b**, *duodenal output of bilirubin during phase II of the IDMC*

Discussion

The motor response of the gallbladder to meals and the hormonal basis for this response were documented almost 60 years ago[8,11–13]. However, in recent years a number of studies have defined much more precisely the pattern of gallbladder contraction and emptying in the postprandial period and have demonstrated for the first time that the gallbladder also contracts at regular intervals during fasting[14–17]. In the postprandial period, gallbladder contraction is triphasic: an initial forceful contraction, occurring within 5 min of starting to eat, is followed by an isotonic contraction phase which lasts for approximately 90 min and this, in turn, is followed by rhythmic, large amplitude contractions which last for 4–6 h[14,16]. Gallbladder emptying is maximal during the first 30 min and is essentially complete within 90–120 min[14]. During fasting, gallbladder contraction coincides with the commencement of phase II of the IDMC in the duodenum[14,15], and 20–25 per cent of gallbladder contents are expelled into the duodenum with each interdigestive contraction[14].

In the present study we wished to determine the effect of vagotomy on these known events and so we utilized methodology which has previously been shown to give accurate results and which allows precise definition and correlation of duodenal and gallbladder motor activity and also precise quantitation of gallbladder emptying[14,18]. The model used does not interfere with normal motor activity or emptying in the gallbladder or duodenum. In this study we have shown that neither selective denervation of the gallbladder nor truncal vagotomy (the more common clinical correlate) significantly alter gallbladder motility in the early postoperative period either during fasting or after food. These findings do not necessarily contradict those of others which suggest that a disturbance of gallbladder motility does, in fact, occur in the long-term after vagotomy[6,7,19,20]. However, we believe that this disturbance may be due to the gradual emergence of other factors related to the vagotomy rather than to a primary effect of gallbladder denervation.

Previous studies on the effects of vagotomy on gallbladder function in humans and in experimental animals[6,7,19,20,21–23] have usually been based on radiological observations of the gallbladder. Although there are some discrepancies in the different results reported there appears to be general agreement that vagotomy is followed by the gradual onset of dilatation of the gallbladder. However, almost all of the previous observations of gallbladder function were made many months after vagotomy, and so it is difficult to state that any changes which were detected were a primary result of vagal denervation since other factors could have gradually affected gallbladder motility over this period, e.g. a change in gallbladder wall compliance, a change in sphincter of Oddi resistance, or a gradual exhaustion of gallbladder contractility due to longstanding elevation of sphincter of Oddi resistance[24–26]. Our studies were performed in the very early postoperative period (as soon as the return of normal gut motility was documented) so that the primary effect of vagal denervation on the gallbladder could be assessed before any of these other factors could have an appreciable secondary effect on gallbladder function. Although one previous study did look at the effect of vagotomy on fasting gallbladder contraction[27], no previous

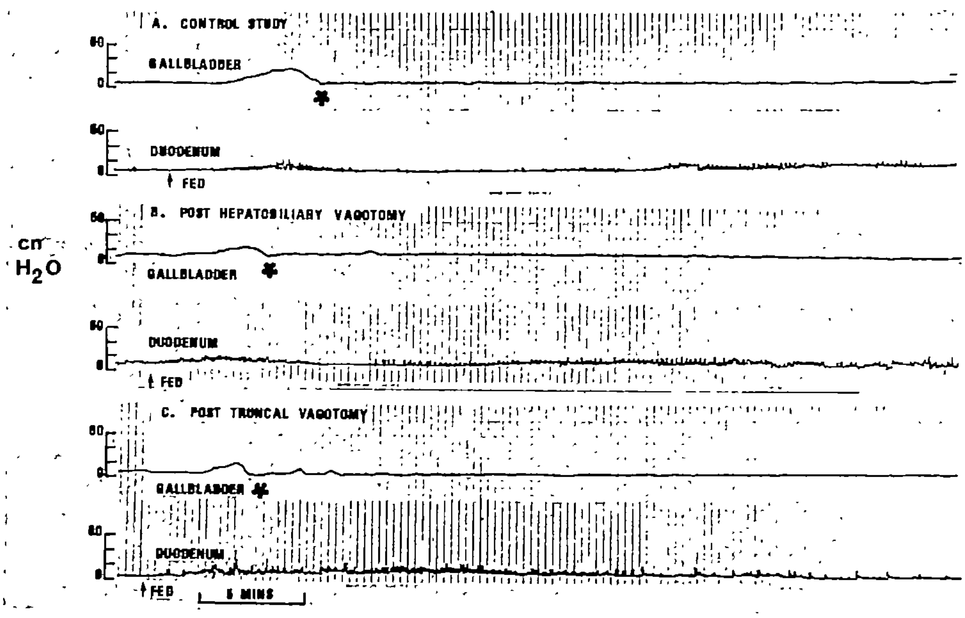

Figure 4 *Simultaneous recording of postprandial gallbladder and duodenal motor activity. Asterisk marks time of first appearance of bile in duodenal contents*

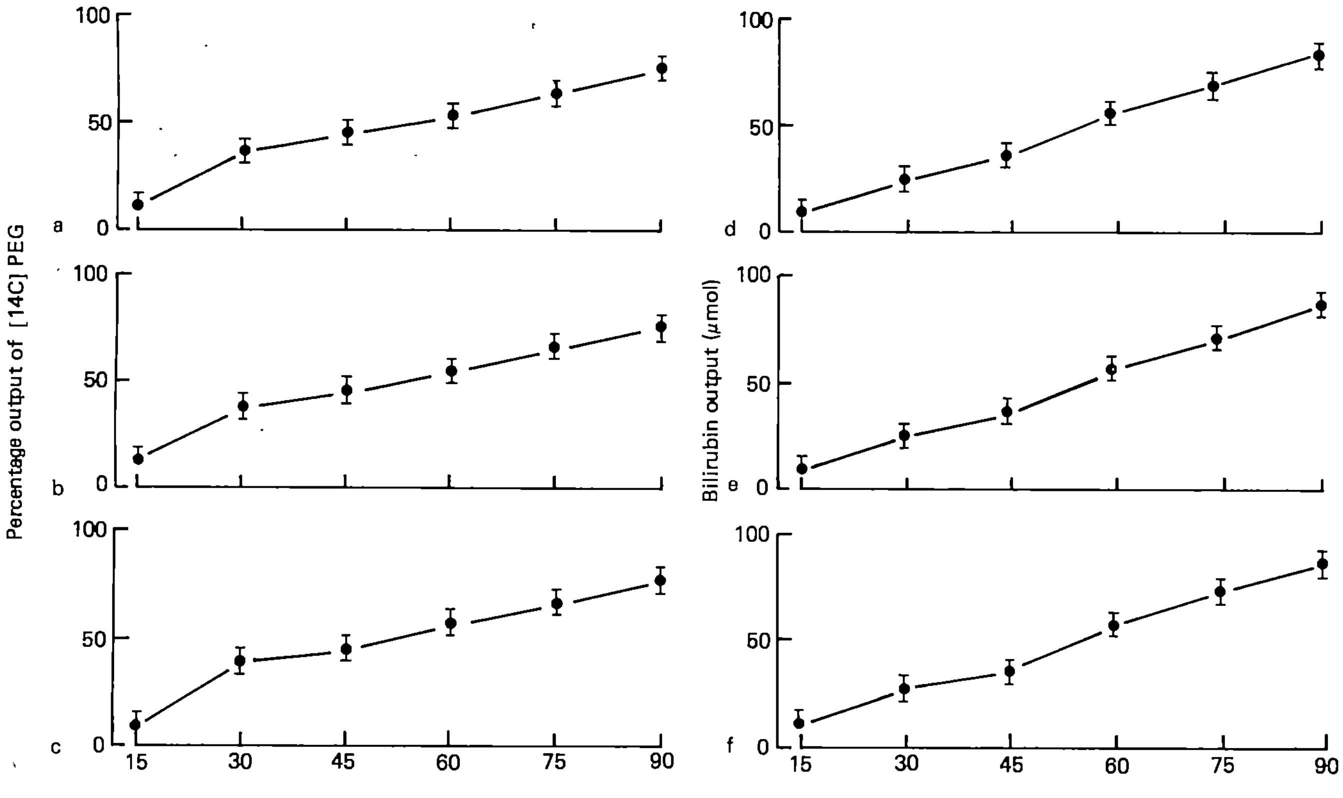

Figure 5 *Postprandial gallbladder emptying (cumulative duodenal output of GB marker,* [^{14}C]*PEG):* **a**, *controls;* **b**, *after hepatobiliary vagotomy,* **c**, *after truncal vagotomy, and postprandial cumulative duodenal output of bilirubin;* **d**, *controls;* **e**, *after hepatobiliary vagotomy;* **f**, *after truncal vagotomy*

study examined gallbladder motility and emptying in relation to the IDMC. However, interdigestive gallbladder motility is probably highly relevant to gallstone formation as the lithogenic index of bile is highest during prolonged fasting[28] and the periodic contraction and partial emptying of the gallbladder which occurs during phase II of the IDMC[14] may play an important role in preventing prolonged stasis of highly concentrated bile.

The precise mechanism by which gallstones may form after truncal vagotomy is uncertain. The possibilities include (i) the development of biliary stasis; (ii) the development of lithogenic bile; (iii) an increase in biliary nucleating factors. The stasis theory has been the most frequently cited possibility, largely because of the radiological studies which show dilatation of the gallbladder after vagotomy. However, the present study has shown that vagotomy *per se* does not affect gallbladder motility in the early postoperative period either during fasting or postprandially, and other studies have confirmed that the gallbladder can contract normally in response to cholecystokinin after vagotomy[22,23]. The function of the vagal supply to the gallbladder and the precise cause of gallstone development after vagotomy therefore remain as unanswered questions. It seems quite possible that the role of the vagus is to coordinate contractile activity throughout the biliary tree so that the sphincter of Oddi relaxes in association with gallbladder contraction. Previous studies have shown persistently elevated tone in the sphincter of Oddi after vagotomy[24,25] and so, although the gallbladder can contract and empty normally in the early postvagotomy period, it does so against increased resistance. It is entirely plausible that in these circumstances the gallbladder will eventually develop 'contractile failure' and become dilated and hypotonic as happens in other smooth muscle organs with longstanding outflow resistance. This would explain the previously observed long-term radiological appearance of the gallbladder after vagotomy and the known predisposition to gallstones. However, this is just one of a number of explanations which await further evaluation.

Acknowledgements

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Short note

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Radiation-induced brachial plexus neuropathy following breast conservation and radical radiotherapy

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During the past decade there has been an increasing tendency to manage early breast cancer by wide local excision of the tumour plus radical radiotherapy to the retained breast and nodal drainage areas. Preliminary results suggest this strategy is as effective as mastectomy. However, the long-term side-effects of irradiation have yet to be fully evaluated.

Brachial plexus neuropathy is an infrequent, but well-documented, complication after mastectomy with radiotherapy, but its incidence after local excision and radiotherapy and its relationship to dose–time irradiation schedules are, as yet, undefined.

We present six cases after local excision with radiotherapy and discuss their implications.

Case reports

Two hundred and fifty patients with early breast cancer were treated by wide local excision and radical radiotherapy at the Royal Marsden Hospital between 1980 and 1983. During routine follow-up, six women (2·4 per cent) developed symptoms of brachial plexus neuropathy within 4–24 months following radiotherapy. The details of these cases are shown in *Table 1*. Each patient received radical radiotherapy to the residual breast tissue, axilla, supraclavicular fossa and internal mammary chain using a Telecobalt unit with a three-field technique. A calculated total dose of 51 Gy was delivered to the region of the brachial plexus in fractions of 3·4 Gy.

Each was thoroughly examined to exclude locoregional recurrence and to define the precise nature of the neurological deficit.

Four patients had neuropathy involving the lower plexus, while the upper plexus was principally affected in the remaining two. All had marked induration of the supraclavicular fossa and axilla. Fine needle aspiration cytology carried out in three cases failed to show the presence of malignant cells. Computed tomography of the brachial plexus performed in three patients showed distortion of the tissue planes around the plexus (*Figure 1*). These appearances were considered to represent radiation-induced fibrosis rather than tumour infiltration. Electromyography in three of those with lower plexus neuropathy localized the site of nerve compression to the brachial plexus rather than to the elbow or carpal tunnel.

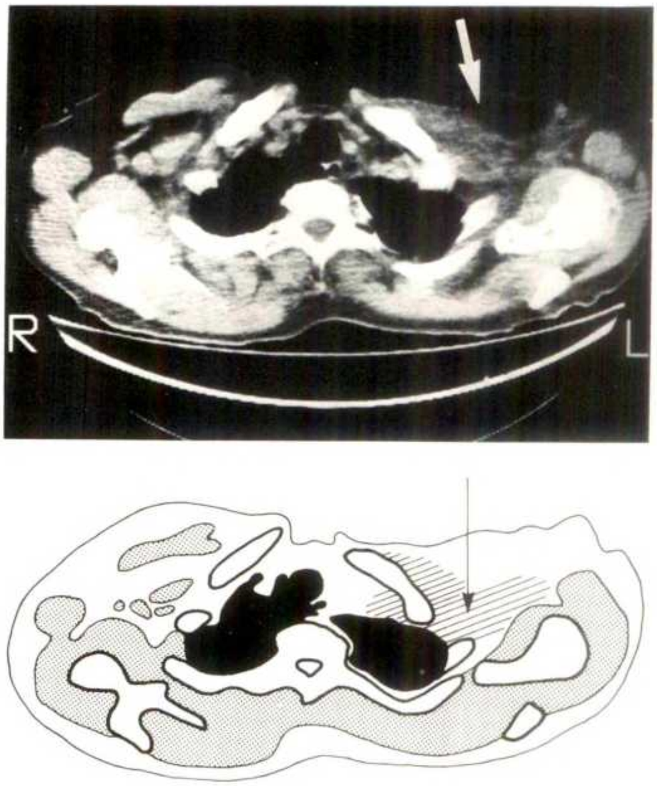

Figure 1 *Case 3: CT scan of brachial plexus. The arrow demonstrates distortion of tissue planes around the brachial plexus due to fibrosis, with some adjacent apical pulmonary fibrosis*

These women have been followed up for between 12 and 48 months from the onset of neurological symptoms, and have remained free of tumour recurrence.

Discussion

Brachial plexus neuropathy may be caused either by malignant infiltration or by radiation-induced fibrosis around the plexus. Some differences in the clinical features of the two groups have been reported, but a confident diagnosis of radiation-induced neuropathy can only be made if the patient remains free of recurrence for many months after the onset of symptoms[1]. Computed tomography of the brachial plexus will differentiate between the presence of a soft tissue mass around the plexus due to recurrent disease, and the diffuse loss of tissue planes due to radiation-induced fibrosis, and is the investigation of choice[2].

Table 1 *Clinical details of the six patients treated by wide local excision, and 51 Gy radiation*

Case	Age	Axilla surgery	Stage	Interval from radiotherapy to neurological symptoms (months)	Portion of brachial plexus affected	Dominant arm affected	Degree of disability	Follow-up since onset of neurological symptoms (months)
1	57	Clearance	$T_2 N_0$	14	Lower	No	Severe	34
2	61	Sample	$T_2 N_1$	12	Lower	No	Mild	36
3	57	Sample	$T_2 N_0$	24	Upper	Yes	Severe	36
4*	41	Sample	$T_1 N_1$†	4	Lower	Yes	Severe	28
5	36	None	$T_1 N_{1b}$	10	Lower	No	Severe	28
6	31	Sample	$T_1 N_1$	6	Upper	No	Mild	54

* Case 4 has previously received 25 Gy, to the neck and mediastinum in 1959 for Stage II Hodgkin's disease without complications
† Clinical assessment

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Once established, radiation-induced neuropathy is difficult to treat. Anti-inflammatory, neurotropic, and vasodilator drugs, physiotherapy, sympathectomy, electrical stimulation, cordotomy, amputation, surgical neurolysis and omental grafting have all been advocated, but frequently fail to provide worthwhile symptomatic improvement.

The distressing symptomatology, problematical diagnosis and disappointing results of therapy for brachial plexus neuropathy indicate that potentially harmful doses of irradiation to the brachial plexus should be avoided. Nervous tissue is more susceptible to late radiation damage than skin and connective tissue[3]. Furthermore, the likelihood of radiation damage to the nervous system appears to be dose dependent. Basso-Ricci *et al.*[1] found that radiation-induced neuropathy occurred in 3·2 per cent of 490 mastectomy patients when the brachial plexus received an estimated 60 Gy (2 Gy per fraction), but in none out of a series of 200 receiving only 49 Gy to the plexus. Wigg *et al.*[3] considered that radiation-induced neuropathy is related to the size of individual fractions as well as the total dose. Thus damage was more frequent when the total dose exceeded 50 Gy and when the dose per fraction was more than 2·5 Gy. The incidence of brachial plexus neuropathy in our series is higher than that reported for most published series of patients undergoing breast conservation and radiotherapy (although this complication is rarely documented), and suggests that the high dose fractionation schedule of 51 Gy in 15 fractions (3·4 Gy per fraction) may be responsible. Our fractionation scheme was adopted because of the demands made on the machine time by the increased number of patients being treated by breast conservation, and was considered equivalent to a conventional schedule delivering 60 Gy in 30 fractions over 6 weeks. The present data suggest that high fractionation schedules should be avoided.

The risk of radiation-induced neuropathy, and other long-term complications of radiotherapy, may justify a more selective policy of axillary and supraclavicular irradiation in patients with breast cancer treated by wide local excision and radiotherapy. Such an approach has recently been advocated by Yarnold[4].

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Case for conservative management of selected fibro-adenomas of the breast

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To assess the safety of a conservative approach to fibro-adenoma of the breast we prospectively studied 321 women with this clinical diagnosis, and performed aspiration cytology and excision biopsy. There was histological confirmation of fibro-adenoma in 217 (68 per cent), the remainder having various benign conditions and 4 (1·3 per cent) had carcinoma. Aspiration cytology had a sensitivity of 87 per cent and a specificity of 76 per cent for fibro-adenoma. Three cases of carcinoma were identified cytologically and the fourth was regarded as suspicious. To estimate the risk of missing carcinoma we compared the annual frequency of carcinoma with fibro-adenoma in young women and found a ratio of 1:470 between 15 and 19 years, 1:133 between 20 and 24 years and 1:9 in the 25–29 age group. To assess patients' views on non-operative treatment of benign breast masses we asked 124 women, 10 days postoperatively, whether they preferred a conservative approach for a cytologically benign lump: 26 (21 per cent) opted for conservative management in the future and 8 (7 per cent) would have preferred conservatism rather than their recent excision. A conservative approach is safe for clinically and cytologically benign breast lumps in women under 25 years, but very few will accept it.

Keywords: Breast diseases, fibro-adenoma, cytodiagnosis, needle biopsy

The traditional surgical approach to discrete breast masses is that they should be excised. If, however, a mass is known to be a fibro-adenoma (FA), there is a good argument for treating it conservatively. These lesions do not predispose to carcinoma[1,2] and transformation to phyllodes tumours is excessively rare, if not highly controversial[1,3]. Their natural history is not certain, but various patterns of behaviour are known: they may remain stable, regress[4] or slowly increase in size[3]. Rapid growth may occur in certain adolescents[5] and occasionally during pregnancy and lactation[6]. Surgical removal carries the potential complications of anaesthesia as well as those of haemorrhage and infection, and the scars, particularly with recurrent or multiple FA, may be disfiguring.

The case for the conservative management of FA rests on the accuracy of diagnosis short of removal for histological examination to exclude malignancy. We therefore set out to evaluate the accuracy of clinical assessment supported by aspiration biopsy for cytology (ABC). In addition, as conservatism has been suggested in younger women we felt it important to quantify the risk of missing a carcinoma in a woman under 30 years who presents with a breast mass suggestive of FA. Finally, we assessed the patients' attitude to a conservative approach using ABC rather than excision.

Patients and methods

Over the 16 months between April 1985 and July 1986 all patients attending the Groote Schuur Hospital Breast Clinic with a mass which might, on clinical grounds, have been FA were studied prospectively. The clinical criteria for making the diagnosis were the presence of a firm circumscribed mass without features to suggest malignancy or an inflammatory process. ABC was performed by two clinicians with experience in this procedure and smears were stained by a modified Papanicolaou technique. The cytologists classified the aspirate as: (i) technically inadequate, (ii) compatible with FA, (iii) benign, not otherwise specified, (iv) suspicious, or (v) malignant. The cytological criterion for the diagnosis of FA was the presence of a cellular aspirate consisting of large branching sheets of uniform epithelial cells on a background of smaller 'stripped' free-lying oval hyperchromatic nuclei from myoepithelial cells. In younger patients a fairly marked degree of atypia, pleomorphism and crowding was compatible with FA. Evidence of apocrine metaplasia and occasional foamy histiocytes were also compatible with FA, but were more usually associated with fibro-adenosis. All lesions were excised for histological examination. Sensitivity and specificity were calculated by accepted methods[7].

To estimate the chance of a carcinoma being confused with a FA in women under 30 years, we extracted from our records all cases of carcinoma in young women registered at our clinic over the decade 1974–1983. We then determined the annual frequency of carcinoma by 5-year age group and compared it with the annual frequency of proven FA from this study. To quantify the theoretical risk of a carcinoma being missed after ABC in this population, we took our absolute sensitivity of ABC for carcinoma to be 96 per cent (i.e. false negative rate of 4 per cent)[8].

To assess our patients' attitude to the conservative management of breast masses, 124 women were interviewed 10 days after excision biopsy. Each woman was told that it was now possible to exclude carcinoma reliably using ABC, without excision of the mass. She was then asked first if she would prefer non-operative management of a similar mass in the future, and second, if she would have preferred non-operative management of her previous mass.

Results

Three hundred and twenty-one women were considered clinically to have FA and entered the study. During this period 2627 new patients were registered at our breast clinic.

The final histology showed the diagnosis to be correct in 217 instances (67·6 per cent) (*Table 1*). The most common lesion to mimic FA was fibro-adenosis in its various forms including sclerosing adenosis and blunt duct adenosis; other mimics were inflammatory lesions, fat necrosis and apparently normal breast tissue. Four patients had breast carcinoma: their ages were 35, 35, 38 and 51 years, and all were subsequently shown to have T_1 or T_2, node-negative disease.

While the clinical diagnosis of possible FA was a prerequisite for eligibility for the study, we compared the FA with the non-

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Table 1 *Final histological diagnosis*

Fibro-adenoma		217 (67·6%)
Fibro-adenosis		54 (16·8%)
Other lesions		46 (14·3%)
Normal	11	
Inflammatory	11	
Fat necrosis	10	
Cysts and galactocoeles	8	
Adipose tissue	3	
Pregnancy adenoma	2	
Phyllodes tumour		
Carcinoma		4 (1·3%)
Total		321

Table 2 *Comparison of final diagnosis with clinical features and cytological diagnosis*

	Fibro-adenoma	Non-fibro-adenoma
Final histology	217	104
Age (mean ± s.d.*)	24·3 ± 8·2	31·7 ± 11·5
range	12–55	13–66
Clinical features		
Mobile, defined, non-tender**	163 (75%)	53 (51%)
Mobile, defined, tender	44 (20%)	25 (24%)
Mobile, poorly defined, non-tender**	10 (5%)	14 (13%)
Other combinations	0	12 (12%)
Cytology		
Not done	29	7
Inadequate***	18	23
Fibro-adenoma	147	18
Benign, not otherwise specified	21	45
Suspicious	2	8 (1 carcinoma)
Malignant	0	3 (3 carcinomas)

* $P<0{\cdot}01$, t test; ** $P<0{\cdot}01$, χ^2 test; *** $P<0{\cdot}05$, χ^2 test

fibro-adenoma populations to identify any features that may have been different (*Table 2*). The age distribution of the two groups was significantly different ($P<0{\cdot}01$), FA occurring predominantly in the 16–32 year group. The clinical features of mobility, a well-defined lump and the absence of tenderness made the diagnosis of FA significantly more likely ($P<0{\cdot}01$), but not exclusively so.

ABC was performed in 285 patients (89 per cent), the remainder either refusing the procedure or having a mass too small for aspiration. Technically inadequate specimens were obtained in 41 instances (14 per cent), (more in the non-fibro-adenoma group, $P<0{\cdot}05$), leaving 244 patients with adequate aspirates for diagnostic purposes. ABC correctly diagnosed FA in 147 of 170 (86 per cent) instances. An incorrect diagnosis of FA was made in 18 cases, (14 fibro-adenosis, 3 apparently normal breast tissue and one with inflammatory changes), and these misinterpretations were due to these specimens showing benign cellular features compatible with those seen with FA. In 66 instances, ABC made the diagnosis of 'benign, not otherwise specified' and was correct in 45 (68 per cent); the remaining 21 cases were FA and this false negative rate was due to the cytological features being of benign breast tissue, but not sufficiently typical to be compatible with a diagnosis of FA. In 10 instances the cytological appearances were suspicious; one of these lesions proved to be a carcinoma, two were FA, and the remainder were other benign conditions. Four patients had carcinoma and ABC correctly diagnosed three as malignant and the fourth as suspicious. There were no false positive diagnoses of carcinoma. Our sensitivity of ABC for FA was therefore 86 per cent and our specificity was 76 per cent.

We identified 29 young women with breast carcinoma over the decade: one was 17 years old, four were between 20 and 24 years and 24 between 25 and 29 years. These patients constituted 1·4 per cent of 2129 patients with breast cancer registered in this period. Nine (31 per cent) had an initial clinical diagnosis of FA. When this age frequency by decade was converted to an annual frequency and compared with that of FA, the ratio carcinoma: FA increased from 1:470 between 15 and 19 years to 1:9 between 25 and 29 years (*Table 3*). Assuming that ABC in our hands would give a 4 per cent false negative rate for carcinoma, we calculated the misdiagnosis rate (assuming all carcinomas had the clinical diagnosis of FA) to be very small under the age of 20, but to rise to one in 229 in the 25–29 age group.

When 124 patients were interviewed after excision of a histologically benign mass 26 (21 per cent) opted for future non-operative management of a similar problem. Only 14 of these women were less than 25 years, an age when the misdiagnosis as carcinoma would be rare. When asked whether they would have preferred their previous breast mass to have been treated conservatively only eight (7 per cent) agreed and of these, four were less than 25 years. Thus only 14 (11 per cent) of the women interviewed were under 25 years, had benign aspirates and agreed to future conservatism; only four (3 per cent) would have similarly preferred conservatism rather than their recent excision.

Discussion

If the case for the conservative management of FA is to be supported it must be shown that either an accurate positive diagnosis of FA can be made, or that a malignant condition can be confidently excluded without surgical removal.

The accuracy of our clinical diagnosis of FA was limited, being correct in only two-thirds of cases. The remaining third consisted of a variety of conditions (including carcinoma) many of which had the well-known features of mobility, good definition and lack of tenderness, characteristic of FA. In their retrospective study of FA, the Edinburgh group found a correct clinical diagnosis in just over one-half of their cases, the balance being made up by mammary dysplasia, but also including a number of cases of carcinoma[9]. Clearly, additional investigation is necessary to improve on clinical assessment.

Additional confirmation with ABC yielded a sensitivity for FA of 86 per cent with a rather low specificity of 76 per cent. In other words, if the lesion was FA, the test was likely to indicate this; if, however, the lesion was not FA, the test could well confuse it with one. This confusion was due to the fact that some benign conditions, particularly fibro-adenosis, may have cytological appearances indistinguishable from FA. The low specificity of cytology for FA does not, however, diminish the precision of ABC in differentiating benign from malignant disease.

An evaluation of the accuracy of ABC in the diagnosis of carcinoma was not part of this study. We have previously found an absolute sensitivity of 96 per cent and specificity of 98 per cent for carcinoma[8]; most centres with a special interest in breast cytology have reported a sensitivity of 90–99 per cent[10,11].

Table 3 *Annual age-related frequencies of carcinoma and fibro-adenoma in young women*

Age (years)	Annual frequency		Ratio CA:FA	Missed carcinoma*
	Carcinoma	Fibro-adenoma		
10–14	0	3	–	–
15–19	0·1	47	1:470	1:11 750
20–24	0·4	53	1:133	1: 3313
25–29	2·4	22	1: 9	1: 229

* Assuming 96% of carcinomas will be detected by ABC

Thus, while cytology may easily confuse other benign conditions with FA, the investigation can detect carcinoma with a high degree of accuracy. This was borne out by the confident diagnosis of three of the carcinomas and the categorization of the fourth as suspicious in this study.

Carcinoma is unusual in women under 30 years of age and this alone would make its misdiagnosis as FA an uncommon event. It has been suggested that FA may be managed conservatively under 25[12] or 35[9] years; in view of the theoretical risks we have shown, we would favour a 25 year cut-off point. This age limit would make less than one-half of our patients eligible for conservative management and this proportion would be further reduced when aspiration was not possible or unsuccessful, as happened in 25 per cent of our cases. Moreover, most of the women who were interviewed preferred excision. This attitude may reflect public awareness campaigns which encourage breast self-examination and the attendance of screening clinics; it may also reflect an inherent fear of malignancy in women with a breast mass.

Thus we believe that a conservative approach is safe in the small proportion of women under 25 years who request it and in whom a technically adequate ABC is unequivocally benign. Patients with large or rapidly growing FA, risk factors for carcinoma or who prefer excision should have surgery. Other patients, particularly those with multiple or recurrent FA and those who are reluctant to undergo surgery may be offered the option of conservative management.

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Thallium–technetium isotope subtraction scanning in primary hyperparathyroidism

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Between January 1983 and March 1986, 75 consecutive patients underwent cervical exploration for primary hyperparathyroidism (HPT). Each patient had a thallium–technetium subtraction isotope scan of the neck, performed pre-operatively. Of 71 patients with technically satisfactory scans, 68 came to 'first-time' neck exploration whilst 3 underwent reoperation for persistent hypercalcaemia. At primary cervical operation, 53 of the 68 patients each had a solitary adenoma as the cause of their HPT. In 28 (53 per cent) of these individuals the scintigram accurately predicted the site of the parathyroid tumour ('helpful' scans). The technique was 'unhelpful' in 17 patients (32 per cent) with false positive scans and in 8 patients (15 per cent) with false negative scans.

There was a highly significant difference between the median weight of adenomas removed from patients with helpful scans (1·05 g) and that of adenomas retrieved from individuals with unhelpful scans (0·47 g), ($P<0{\cdot}001$).

Since 1 January 1985 we have adopted a policy of 'scan-directed' unilateral neck exploration for patients with HPT on the basis of solitary adenoma and in whom the isotope scan was positive. The mean operating time for these patients ($n=18$, mean operating time 1·24 h) was significantly shorter than that for patients with unhelpful scans ($n=14$, mean operating time 1·55 h, $P<0{\cdot}01$) who were submitted to standard bilateral cervical operation.

Subtraction scanning was helpful, in terms of localization of enlarged parathyroid glands, in only three of eight patients with multigland hyperplasia. The investigation was of positive help in locating the adenoma in two of three individuals submitted to cervical re-exploration for persistent HPT.

Mediastinal parathyroid tumours

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Most normal and abnormal parathyroid glands are situated near the posterior lateral capsule of the thyroid gland, but they may also be situated in the anterior or posterior mediastinum or in other ectopic positions.

From January 1981 to 31 December 1986, 286 operations were performed in 284 patients with hyperparathyroidism (246 primary, 38 secondary and 53 reoperations). Of these patients, 64 had abnormal parathyroid glands situated in the mediastinum (52 anterior and 12 posterior). A total of 39 of the mediastinal tumours were adenomas and 25 were hyperplastic glands. Mediastinal tumours were responsible for 18 cases requiring reoperation (17 referred from other hospitals). In four patients, the mediastinal tumour was a fifth histologically documented parathyroid gland (two hyperplasia, two adenoma). Mediastinal tumours were identified by pre-operative localization studies (sonography, CT or MRI scanning, thallium–technetium scanning and selective venous catheterization for parathyroid hormone (PTH) assay) in 11 of the 18 patients requiring reoperation, although the various tests often gave discrepant results. When the tumour localized pre-operatively only one patient required a median sternotomy; this was because the atypical parathyroid adenoma was situated deeply within the anterior mediastinum and was supplied by the innominate artery rather than by the inferior thyroid artery. Median sternotomy was performed in nine patients and abnormal parathyroid tissue was identified in seven of these patients (one failed case had a solitary metastasis from parathyroid cancer in the liver and the other had a PTH secreting squamous cell carcinoma).

In conclusion, mediastinal parathyroid tumours were present in 64/286 patients (22 per cent) with hyperparathyroidism, and in 18/53 patients (34 per cent) requiring reoperation for persistent or recurrent hyperparathyroidism. Most mediastinal parathyroid tumours may be removed by a cervical incision, especially if localized pre-operatively.

Dynamic tests of parathyroid function for diagnosis of primary hyperparathyroidism

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Hypercalcaemia is most commonly due to primary hyperparathyroidism (HPT) or malignancy and an accurate discrimination is often not possible from basal measurements of calcium and parathyroid hormone (PTH) concentrations alone. We have utilized hypocalcaemic tests to differentiate HPT from other causes of hypercalcaemia and to diagnose HPT in patients with malignancy.

The material consists of 49 patients with surgically verified primary HPT, 18 patients with hypercalcaemia of other origin (malignancy, sarcoidosis, immobilization, thyrotoxicosis) and 8 patients with primary HPT together with disseminated malignancy. Total serum calcium values were 2·72–4·11 mmol l^{-1} (reference range 2·20–2·60 mmol l^{-1}) and mid-C regional immunoassay (S 478) disclosed elevated PTH values in 31 of the HPT patients and 9 of those with other causes of hypercalcaemia. Twenty-six healthy controls were also investigated.

The subjects were given a constant EDTA infusion (24 mg kg^{-1} h^{-1}) for 30–60 min or a single IM injection of 100 units salmon calcitonin for analysis of ionized calcium and PTH every 5–10 min (EDTA) or after 7·5–8 h (calcitonin).

EDTA infusion induced linear decrease in ionized calcium. In HPT this was invariably associated with increments of PTH already within the hypercalcaemic range. This distinguished half of the HPT patients with normal basal PTH values from the normal controls. Calcitonin injection induced reductions of ionized calcium (3–5 per cent) in 47/50 cases. This was accompanied by increments in PTH in 18/20 patients with HPT. It could not be used to differentiate mild HPT from normal controls. Patients with hypercalcaemia unrelated to HPT responded with PTH elevations only when ionized calcium was reduced far into or below the normal range. HPT was diagnosed in all patients with concomitant malignancy.

Dynamic tests of parathyroid function seem valuable for differential diagnosis of hypercalcaemia.

β_2 microglobulin urine to serum ratio: an early marker of renal dysfunction in primary hyperparathyroidism

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The correct treatment of asymptomatic primary hyperparathyroidism remains unclear and opinions differ as to the management in such cases when there is no evidence of renal dysfunction or tissue calcification. The β_2 microglobulin (B_2 M) urine to serum ratio was measured in 22 patients with primary hyperparathyroidism (15 pre-operative and 7 treated conservatively) in addition to 20 age and sex matched control subjects. The ratio was found to be significantly higher in cases of hyperparathyroidism compared to controls ($P<0{\cdot}01$ Mann–Whitney U test). Creatinine clearance remained within normal limits in all patients. Following surgical excision of a parathyroid adenoma in 15 cases, the B_2 M urine to serum ratio fell to normal limits.

Table *Urine and serum β_2 M concentration (mean and range μg/l) in patients with primary hyperparathyroidism and normal subjects*

	Number	Urine	Serum	Urine/serum ratio (×100)
Pre-operative	9	160	1360	11
		60–200	890–2520	4–22
No operation	7	357	1893	18
		76–1332	1013–3747	5–35
Postoperative	9	60	1820	4
		30–130	1630–1980	2–7
Normal subjects	20	80	1984	3
		70–100	1700–1200	1–5

It is uncertain whether the changes are a feature of hypercalcaemia *per se* or a direct result of excess parathormone activity. These changes should not be regarded as an argument against the conservative management of mild primary hyperparathyroidism but rather as a further indication for careful long-term follow-up of patients managed in this way.

Hypertension and renal dysfunction in primary hyperparathyroidism: the effect of parathyroidectomy

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The pathogenesis of the hypertension which may accompany hyperparathyroidism and the effect of parathyroidectomy on blood pressure and renal function is not clear.

A total of 24 patients with primary hyperparathyroidism were studied before, and 18 of them restudied 6·5 months (mean) after parathyroidectomy. Comparison was made with age and sex matched patients with essential hypertension and with normotensive control subjects.

There was a significant inverse relationship between mean arterial pressure and ^{51}Cr EDTA clearance in patients with hyperparathyroidism both pre- ($r = 0{\cdot}476$, $P < 0{\cdot}05$) and postparathyroidectomy ($r = -0{\cdot}75$, $P = 0{\cdot}0003$), but not in essential hypertensives—suggesting a pathogenic role for impairment of renal function in the hypertension of hyperparathyroidism. Creatinine clearance (C_{Cr}) appeared to overestimate glomerular filtration rate (GFR) in patients with hyperparathyroidism, falling significantly after surgery while ^{51}Cr EDTA clearance was unchanged. This overestimate of GFR by C_{Cr} may account for the failure of some previous studies to relate hypertension to impairment of renal function. Plasma renin activity, plasma aldosterone, and total body exchangeable sodium did not differ in normotensive and hypertensive patients with primary hyperparathyroidism and were unchanged after surgery. Parathyroidectomy did not result in any change in blood pressure or in CGR measured by ^{51}Cr EDTA clearance. The failure of surgery to reverse established changes in blood pressure and renal function provides an argument for early intervention to prevent renal damage.

Outcome of surgery for Graves' disease in the North-east of Scotland re-examined

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Subtotal thyroidectomy for Graves' disease was carried out in 161 patients during the years 1976–1985. The immediate postoperative morbidity was low and the mortality zero.

Data were available for 80 patients with a 5-year follow-up. The prevalence of hypothyroidism increased throughout the 5-year period. Patients who developed subclinical failure (low serum T4 and/or high TSH) in the first postoperative year were at increased risk of subsequently developing clinical failure, although 75 per cent of them did not. Despite an expectant policy all patients with clinical failure confirmed biochemically ultimately required replacement thyroxine.

There was a strong negative correlation between remnant weight and the development of hypothyroidism at both 1 and 5 years. A relationship was not found between remnant weight and recurrent toxicity. Patients with a total gland weight <50 g had a significantly increased prevalence of recurrent toxicity ($P < 0{\cdot}05$).

These results have prompted changes in local policy. The optimum remnant weight is now suggested to be 9–10 g if the total gland weight is >50 g. When the gland weight is <50 g and other treatment options have been exhausted, operation leaving a small (2–4 g) remnant is suggested accepting the high risk of subsequent thyroid failure. Replacement therapy will be avoided in the first three postoperative months but clinical failure at 4 months or later will be a definite indication for it.

Follow-up remains lifelong for all patients.

Management of retrosternal goitre

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In the period 1977–1987, 885 thyroidectomy procedures were performed in one surgical unit at the University Hospital of Wales. In 67 patients (47 women, 20 men, F:M = 2·35:1) the surgery was for retrosternal goitre. The mean age of this group was 58·5 years and most had a longstanding goitre with the longest history being 50 years.

A total of 58 patients were symptomatic (87 per cent) and symptoms included airway compression 30, 'asthma' 6, dysphagia 19, hoarseness 15, thyrotoxicosis 8. Two pre-operative recurrent nerve palsies were present in patients with benign multinodular goitres and one patient had superior vena cava obstruction. Surgery was performed through a cervical incision in 65 patients and consisted of bilateral subtotal thyroidectomy (34), unilateral lobectomy (30), biopsy followed by radiotherapy (1). Two patients required both a cervical approach and median sternotomy.

Malignancy was found in seven glands (10·5 per cent) (one follicular carcinoma, two medullary carcinomas, three lymphomas, one secondary carcinoma). Remaining histology was multinodular colloid 50, solitary colloid or follicular adenoma 7, thyroiditis 2, dyshormonogenetic 1. No deaths occurred but complications were, one superficial wound haematoma, one deep haematoma, one DVT, two recurrent nerve palsies and one hypoparathyroidism. All patients were rendered asymptomatic.

We conclude that the presence of a retrosternal goitre is an indication for surgery as there is a serious risk of progressive airway obstruction, there is no alternative medical treatment and malignancy in these glands is not accessible to needle biopsy.

Hypocalcaemia following thyroid surgery

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Hypocalcaemia after thyroid surgery is well recognized[1–3]. Injury devascularization or inadvertent removal of parathyroid tissue may be important factors[4]. Omitting lateral ligation of the inferior thyroid artery and tying small vessels close to the thyroid has been advocated to avoid parathyroid devascularization.

The aim of this study was to determine whether the magnitude of postoperative calcium fall (defined as hypocalcaemia at levels below 2·2 mmol/l) could be modified by: improved parathyroid visualization, groups 1 and 2; and ligation of branches of the inferior thyroid artery close to the gland, group 3.

All patients had pre- and postoperative laryngoscopies, fasting calciums corrected for albumin and a non-fasting calcium at 1 month. Patients had peroperative cystalloid fluid and, in groups 2 and 3, methylene blue was infused at a dose of 5 mg/kg in 500 ml saline.

Patients included were controlled thyrotoxics who underwent thyroidectomy and patients with non-toxic nodules who had lobectomies.

In group 1 (no methylene blue, lateral tie) 25 thyroidectomies and 26 lobectomies were carried out; in group 2 (methylene blue, lateral tie) 25 thyroidectomies and 23 lobectomies; and in group 3 (methylene blue, ties close to the gland) 21 thyroidectomies and 24 lobectomies.

Parathyroid recognition was improved in group 2 (χ^2 test with Yates' correction, $P < 0{\cdot}001$). In all groups a postoperative fall in calcium was seen (Student's t test, $P < 0{\cdot}001$) but there was no statistically significant difference in serum calcium between the groups at comparable times. Morbidity was higher in group 3; in this group there were three transient recurrent laryngeal nerve palsies.

Failure to influence postoperative calcium fall, despite improved visualization of the parathyroids, suggests that surgical trauma plays only a minor role in the development of hypocalcaemia. Tying the inferior thyroid artery close to the gland conveys no benefit and morbidity is higher.

1. Surge DD, Drury MI, McEvoy M, Hefferman SJ, O'Malley E. Long term follow-up of hyperthyroid patients treated by thyroidectomy. *Br J Surg* 1983; **70**: 408–11.
2. Percival RC, Hargreaves AW, Kanis JA. The mechanism of hypocalcaemia following thyroidectomy. *Acta Endocrinol (Copenh)* 1985; **109**: 220–6.
3. Ramus NI. Hypocalcaemia after subtotal thyroidectomy for thyrotoxicosis. *Br J Surg* 1984; **71**: 589–90.
4. Edis AJ. Prevention and management of complications associated with thyroid and parathyroid surgery. *Surg Clin North Am* 1979; **59**: 83–92.

MEA I and MEA II: are they distinct entities?

A. B. S. Ball, C. L. Brown and H. H. Thompson, *The London Hospital, London, E1 1BB, UK*

MEA I and MEA II are usually considered as distinct syndromes, although cases exhibiting overlap have been described. A patient with medullary carcinoma of the thyroid (MCT) and an insulinoma is presented; a combination of pathologies not previously reported.

Case report. A Caucasian woman underwent removal of an insulinoma following hypoglycaemic attacks in 1961, aged 55 years. A vagotomy and pyloroplasty for duodenal ulcer was performed in 1966. There was no family history of endocrine disease. In 1980 she presented with a cold nodule in the right lobe of the thyroid. Surgery was initially withheld because of cardiac problems but in 1982 the swelling increased in size and she developed pressure symptoms. Biopsy of an enlarged cervical lymph node showed metastatic MCT. Serum calcitonin was elevated. A total thyroidectomy was undertaken, after which she remained well for a year. Subsequent recurrence required radiotherapy and two further operations to relieve symptoms. She developed pulmonary metastases and died in 1984, aged 78. Post-mortem examination confirmed MCT and also revealed adrenal medullary hyperplasia and a small phaeochromocytoma.

It is possible that the combination of tumours occurring in this patient is a coincidental finding. However, the case may lend support to the view that MEA I and MEA II are not discrete entities.

Anderson's syndrome with pseudohyperparathyroidism

C. Proye, P. Fossati, D. Ben Soussan, J. L. Wemeau, A. Racadot, J. C. Fourlinnie and E. Imbenotte, *Cité Hospitalière, Lille, France*

A 63-year-old patient experienced hypoglycaemic coma with inappropriately normal immunoreactive insulin levels. Physical examination revealed a huge right adrenal tumour, with no evidence of excess steroid secretion. At operation a 2·2 kg adrenocortical tumour was removed. Despite a histological diagnosis of malignancy the patient remains well 7 years later[1].

The association of an adrenal tumour with hypoglycaemia is Anderson's syndrome[2], 24 cases of which have been reported to date.

The unique feature of this case was the simultaneous occurrence of hypoglycaemia, symptomless hypercalcaemia and hypophosphataemia reversed by surgery. Biochemical analysis of the tumour failed to discover any non-supressible insulin-like activity or hypercalcaemic factor.

Review of the literature discovered only one case of hypercalcaemia associated with an adrenal tumour[3], and two cases of tumour associated hypoglycaemia and hypercalcaemia (one with a hepatoma[4], the other with a pleuromesothelial tumour[5]).

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5. Thomas JJ. *L'Hypoglycémie Organique Tumorale Non Pancréatique.* Thèse Médicine Lille, 1978.

Endoscopic ultrasonography in the detection of insulinomas

P. Shorvon, R. Frost, R. C. G. Russell and W. R. Lees, *The Middlesex Hospital, London W1N 8AA, UK*

Endoscopic ultrasonography (EUS) is a new technique in which a fibreoptic endoscope is specially constructed to incorporate an ultrasound probe in its tip. High resolution real-time images of the pancreas are obtained by scanning from within the duodenal loop and the stomach, and the whole procedure is no more invasive than ordinary duodenoscopy with a side-viewing instrument. The pancreas can be visualized in virtually all patients because the problem of intraluminal bowel gas is avoided.

We have used the technique on eight consecutive patients presenting with clinical and biochemical features of an insulinoma. An insulinoma was successfully localized in all patients, confirmed by subsequent surgery.

Computed tomography (CT) was performed on all patients: despite a specially tailored technique for endocrine tumours, CT only successfully localized two of the tumours.

One of the patients had a previously unsuccessful surgical exploration after angiography had localized the tumour in the head of the pancreas; EUS demonstrated the tumour to be in the uncinate lobe. In another patient EUS had demonstrated two insulinomas; on sectioning of the pancreas following partial pancreatectomy a small insulinoma was discovered.

One patient was demonstrated by EUS to have unsuspected coeliac axis nodal metastases. A malignant insulinoma was confirmed at surgery.

We conclude that EUS is a simple technique which shows considerable promise in the localization of insulinomas, and may prove to be the technique of choice.

Pancreatic islet transplantation effects on diurnal, hormonal and metabolic profiles

T. N. Walsh, D. Alderson, K. G. M. M. Alberti and J. R. Farndon, *St Vincent's Hospital, Dublin, Ireland and University of Newcastle upon Tyne, Newcastle upon Tyne, UK*

Dispersed pancreatic islet transplantation corrects intermediary metabolism in the fasting state[1]. Diurnal profiles after islet transplantation have not been examined. Diabetic complications probably relate to persistent metabolic abnormalities during conventional insulin therapy. This study examines the ability of dispersed islet grafts to correct these diurnal abnormalities. Three groups of dogs were studied: group 1 ($n=12$) normal controls, group 2 ($n=7$) pancreatectomized diabetic dogs receiving twice daily insulin with meals, and group 3 ($n=6$) recipients of a dispersed islet autograft. Blood was sampled every 2 hours from 06.00 to 22.00 hours for a wide range of carbohydrate, protein and lipid metabolites, and insulin concentrations. Meals were given at 10.00 and 16.00 hours and additional samples were drawn in the 2-hour postprandial period. Results were analysed by two-way analysis of variance.

Dispersed islet graft recipients had identical insulin and intermediary metabolite profiles to normal animals. Slight glucose intolerance was observed. Insulin treated animals had near normal mean glucose profiles, but insulin levels were grossly elevated for most of the day. Abnormal levels of all intermediary metabolites were seen in the fasting state and in carbohydrate intermediaries in the postabsorptive state. Dispersed islet grafts can restore intermediary metabolism to near normal. This cannot be achieved by conventional insulin therapy. Such grafts may be expected to prevent the secondary complications of insulin dependent diabetes.

1. Alderson D, Walsh TN, Farndon JR. Islet cell transplantation in diabetic dogs: studies of graft function and storage. *Br J Surg* 1984; **71**: 756–60.

Asymptomatic adrenal masses

G. Favia, F. Lumachi, F. G. Musajo and D. D'Amico, *Universita degli Studi di Padova, Padova, Italy*

During the years 1980–1986, 68 patients underwent surgery with a diagnosis of adrenal disease. Of these, 61 had medullary or cortical hyperfunction (13 phaeochromocytoma, 22 Conn's syndrome, 26 Cushing's syndrome—13 bilateral hyperplasia, 11 adenomas, 2 carcinomas) and 7 (10·3 per cent) a non-functioning tumour. Of the non-functioning tumours, three were malignant (two phaeochromocytoma, one cortical carcinoma). None of the seven patients had hypertension or elevated urinary catecholamine, vanilmandelic acid, aldosterone, free-cortisol, 17 hydroxycorticosteroids or 17 ketosteroids levels. The adrenal mass was always discovered as an incidental finding during CT scanning or ultrasonography for unrelated pathology[1]. All were larger than 3 cm diameter.

All patients underwent primary adrenalectomy, five through a loin incision and two through a midline laparotomy. One patient subsequently underwent a pulmonary lobectomy for a metastasis from a malignant phaeochromocytoma.

No major perioperative complications were observed. At 80–4 months follow-up six patients are still alive and one patient has died.

Our experience indicates that non-functioning adrenal masses larger than 3 cm may be frequently malignant and careful surgical treatment is required.

1. Prinz RA *et al.* Incidental asymptomatic adrenal masses detected by computed tomographic scanning. *JAMA* 1982; **248**: 701–4.

Hypertension in Conn's syndrome and the response to surgery

W. J. Crisp, R. Wilkinson, J. R. Farndon and I. D. A. Johnston, *University of Newcastle upon Tyne, Newcastle upon Tyne, UK*

Hypertension in primary aldosteronism has been reported as mild or moderate; it has been suggested that the hypertension is amenable to medical treatment and that the response to medication is more predictable than the response to surgery. A review of 26 patients (1966–1986) with Conn's syndrome due to solitary adenoma indicated that the diastolic pressure was 125±24 s.d. and the systolic 213±24 s.d. Hypertension in these patients was classified as severe. Hypertension was present for a mean of 4·2 years before the adrenal tumour was diagnosed. Blood pressure was restored towards normal, preoperatively, with a combination of Spironolactone and antihypertensive therapy. In all, 72 per cent of the patients were off all antihypertensive drugs and had normal blood pressures 3 months postoperatively.

These studies confirm that, the hypertension in Conn's syndrome is often severe. The results of surgery are good with 70 per cent of patients not requiring hypertensive therapy at 5 years. In the remaining 30 per cent the hypertension was controlled more easily than before surgery.

Psychiatric morbidity in primary hyperparathyroidism before and after surgery

Susan J. McAllion and C. R. Paterson, *University of Dundee, Dundee, UK*

Over the past 20 years clinicians have been increasingly aware of psychiatric symptoms in patients with primary hyperparathyroidism. However, to date no systematic objective assessment of these symptoms has been carried out.

We have applied a standardized psychiatric interview to 12 patients before and after parathyroidectomy. In this group ten patients had a lower 'psychiatric score' (less psychiatric morbidity) after surgery. There was an improvement in symptoms of fatigue, depression, irritability and sleep disturbance. Ability to concentrate was improved. The levels of intellectual impairment and of anxiety were unchanged after surgery.

The 'psychiatric score' of a group of 24 hyperparathyroid patients, in whom a decision to treat conservatively had been made, was similar to that in the surgically treated patients after surgery.

Psychiatric symptomatology in primary hyperparathyroidism

C. Joborn, H. Johansson, J. Rastad, J. Hetta, H. Agren, G. Akerstrom and S. Ljunghall, *University Hospital, S-751 Uppsala, Sweden*

Patients with primary hyperparathyroidism (HPT) often present with diffuse psychiatric disturbances, but few studies have focused on this aspect of HPT. We have investigated psychiatric symptomatology among unselected patients with primary HPT associated with mild to moderate hypercalcaemia.

In a retrospective study of 441 patients operated on for primary HPT, psychiatric symptoms, mostly depressive or anxiety states, were found in 23 per cent of the patients. The severity of psychiatric symptoms was uncorrelated to the serum calcium levels. Among the older patients, 13 had severe mental disturbances and diagnosis of senile dementia. In all, 8 of these 13 patients, with less than 2 years of severe mental symptoms, were considerably improved after parathyroid surgery and could be transferred to their homes or to somatic units.

In a prospective study of 32 HPT patients, the psychiatric symptoms were investigated by the Comprehensive Psychopathological Rating Scale (CPRS). The HPT patients had pronounced psychiatric symptomatology (CRPS score 17·2±9·0) compared with ten healthy controls (CPRS score 4·4±2·0). Mental symptoms, mostly of a depressive character, were present in almost all patients though half of them had no spontaneous reports of such disturbances. There was no correlation between the severity of symptoms and levels of serum calcium or parathyroid hormone. Lumbar punctures were performed in 26 patients. Analysis of monoamine metabolites in the cerebrospinal fluid (CSF) revealed five HIAA and HVA values below the reference range of half of the patients, i.e. similar to findings in endogenous depression.

At follow-up, 1 year postoperatively, the patients displayed a marked improvement in mental health (CPRS score 4·4±3·0) together with a significant increase in CSF concentrations of five HIAA and HVA.

In conclusion, psychiatric disturbances, which can be improved/normalized by parathyroid surgery, are common in HPT but easily overlooked. The hyperparathyroid state seems to be related to changes in the central nervous system turnover of monoamines, possibly of importance for the symptomatology.

Clinical, biochemical and pathological variables in primary hyperparathyroidism

A. M. El Swais, J. R. Farndon and I. D. A. Johnston, *University of Newcastle upon Tyne, Newcastle upon Tyne, UK*

The clinical presentation of patients with primary hyperparathyroidism (PHPT) is very variable. One patient may be asymptomatic with no evidence of bone or renal disease while another, with exactly the same degree of biochemical disturbance and the same pathology (size and histology), may have severe bone disease or a long history of renal calculi with functional impairment.

This study attempts to analyse clinical, biochemical and pathological variables in 209 patients (162 women) with PHPT according to their mode of presentation: group 1, renal problems; group 2, bone problems; group 3, renal and bone problems; group 4, symptomatic but without apparent renal or bone pathology; and group 5, truly asymptomatic.

Table *Patient variables*

Group	1	2	3	4	5
n	91	17	15	76	10
Mean age (years)	49·2	64·6	58·7	56·6	53·7
Serum Ca (mmol/l)	3·01	3·21	3·16	3·02	2·99
Adenoma/hyperplasia	17/1	16/1	7/1	4/1*	3/1*
Mean gland weight (g)	1·47	4·22*	5·58*	2·18	2·16

* $P<0{\cdot}01$, remaining results not significant

There were no differences in the proportions of groups in different age cohorts and the sex distribution was the same in each group. Preoperative serum calcium correlated slightly with the weight of abnormal parathyroid tissue.

In conclusion, patients with bone disease (groups 2 and 3) have heavier abnormal parathyroid glands, the incidence of hyperplasia is higher in those with asymptomatic or uncomplicated disease (groups 4 and 5) but there are no other biochemical or clinical parameters to explain the protean presentation of PHPT.

Pancreatitis and primary hyperparathyroidism

C. Proye, T. Marmousez, P. Tiry, A. C. L. Richardson, J. L. Wemeau and E. Rwamasirabo, *Cité Hospitalière, Lille, France*

Amongst 500 neck explorations for hyperparathyroidism (HPT), 403 were done for primary HPT. In this group we have seen 14 cases of pancreatitis (4 acute, 1 acute relapsing, 1 subacute, 2 subacute relapsing, 1 biochemical, 5 patients with calcified pancreas). In ten cases the HPT was recognized because of pancreatitis; four patients had some past history of pancreatitis. Only three patients presented with chronic alcoholism. No patient had objective evidence of biliary calculi on cholangiography, cholecystography or ultrasound.

None of these patients have had a laparotomy. All have had neck explorations. The excision of one or more pathological parathyroids has resulted in the cure, clinically and biochemically, of six cases (four acute, one acute relapsing, one subacute). In five of the eight other cases we have noted an improvement in their degree of pain, but four became diabetic and two underwent left pancreatectomy for segmental portal hypertension.

Unfortunately at the present time no physiological or experimental evidence is available to support a causal relationship between primary HPT and pancreatitis. Nevertheless, we are able to make a number of practical conclusions.

All cases of pancreatitis should have at least calcium and phosphate levels measured. Phosphate and chloride levels should be assessed in cases of 'normocalcaemic' acute pancreatitis. Also, pancreatic pathology should be sought in all cases of primary HPT presenting with gastrointestinal symptoms. Finally, when a case of pancreatitis has been proved to be associated with a concomitant primary HPT, the neck explorations should be performed before invasive investigation or operative treatment of the pancreatitis.

Monoclonal antiparathyroid antibodies revealing a defect expression of a calcium receptor in primary hyperparathyroidism

C. Juhlin, G. Akerstrom, E. Gylfe, R. Holmdahl, H. Johansson, R. Larsson, P. Nygren, J. Rastad and L. Klareskog, *University Hospital, S-751 85 Uppsala, Sweden*

This paper reports the production of monoclonal antiparathyroid antibodies with the ability to recognize a unique mechanism for calcium sensing and/or gating in parathyroid cells. The antibodies could also be utilized further to explore mechanisms for a defective hormone regulation in the parathyroid tissue of patients with primary hyperparathyroidism (HPT).

Material and methods. The antibodies were produced by a hybridoma technique after mouse immunization with intact human parathyroid cells and screening for specific reactivity by immunohistochemistry. The function of the parathyroid cell surface structure, recognized by the produced antiparathyroid antibodies, was investigated in a microfluorimetric system enabling studies of the regulation of the cytosolic calcium activity in single normal human parathyroid cells.

A possible difference between normal *versus* abnormal parathyroid tissue in the binding capacity for the antibodies was investigated by immunohistochemistry. The functional consequences of an antibody binding to the parathyroid was further investigated in cells dispersed from the abnormal parathyroid tissue, by registration of the calcium regulated cytosolic calcium activity as well as the parathyroid hormone (PTH) release, measured by immunoassay.

Results. As a result of the immunization and hybridoma procedure three IgG antibodies were produced with the ability to bind exclusively to cell surface structures of parathyroid cells and proximal renal tubular cells. Two of the antibodies were found to interfere in a competitive way with calcium with the cytosolic calcium regulation of parathyroid cells, suggesting that they recognize a putative calcium receptor on the cell surface. By immunohistochemistry the antibodies were found to bind to a lesser extent to the abnormal parathyroid tissue of HPT patients, compared with a high degree of binding to normal parathyroid tissue. Corroborating the interpretation that the antibodies recognize a calcium receptor mechanism of the parathyroid cells was the result of the functional studies of the dispersed abnormal parathyroid cells, where an antibody binding could completely block the effects of calcium on the regulation of the cytosolic calcium activity and PTH release.

In conclusion, the produced monoclonal antibodies evidently substantiate the presence of a unique receptor mechanism for calcium on the parathyroid cells. A decreased expression of this receptor mechanism seems to explain the defective PTH regulation which is characteristic for the parathyroid tissue of HPT patients.

Correspondence

Endoscopic management of common duct stones without cholecystectomy

Sir

We read with interest the paper by D. F. Martin and D. E. F. Tweedle (*Br J Surg* 1987; 74: 209–11).

While agreeing with their conclusion, we wish to differ from their view that 'for patients in whom common duct clearance is unsuccessful ... elective surgery must be the preferred treatment.' We would like to point out an effective and safe, non-surgical alternative for ductal clearance after endoscopic sphincterotomy has failed: percutaneous transhepatic removal[1] or lithotripsy[2]. In our hands this method has cleared, without complications, common bile duct stones in 20 patients with or without endoscopic sphincterotomy. We have also found that a percutaneous biliary drainage procedure, an initial step in transhepatic lithotripsy, is much less hazardous for benign causes than for malignant disease[3].

We would appreciate it very much if this alternative treatment could be brought to the attention of your readers.

C. S. Ho
C. N. Yee
B. Taylor

Toronto General Hospital
Toronto
Canada

1. Clouse ME, Stokes KR, Lee RGL *et al.* Bile duct stones: percutaneous transhepatic removal. *Radiology* 1986; **160**: 525–9.
2. Taylor B, Ho CS. Non-operative management of common bile duct stones. *Can J Surg* 1984; **27**: 28–32.
3. Yee AC, Ho CS. Complications of percutaneous biliary drainage: benign *versus* malignant disease. *AJR* 1987 (In Press).

Author's reply

Sir

We thank Drs Ho and Yee and Mr Taylor for their interest in our paper and for their comments on our discussion. As confirmed by their own paper[1], experience with the technique of percutaneous transhepatic extraction of common duct stones is limited and has only been performed on highly selected patients by enthusiastic operators.

We agree that, if endoscopic extraction of stones in the bile ducts fails, there are other non-surgical techniques available and we have experience of perendoscopic mechanical lithotripsy and the use of dissolution agents instilled via a pernasal biliary catheter. We are not impressed by the results of either of these techniques with the equipment presently available. Extracorporeal shockwave lithotripsy may ultimately replace all these methods when extraction fails[2].

Or course, the presence of the gallbladder may alter the preferred method of management after endoscopic extraction has failed. Only time and experience will supply the answers to these questions, but it is the duty of all who use these techniques to evaluate them fully and openly in order to compare them fairly.

D. Martin
D. Tweedle

University Hospital of South Manchester
Manchester
UK

1. Taylor B, Ho CS. Non-operative management of common bile duct stones. *Can J Surg* 1984; **27**: 28–32.
2. Sauerbruch T, Delius M, Paumgartner G *et al.* Fragmentation of gall stones by extracorporeal shock waves. *N Engl J Med* 1986; 314: 818–22.

Management of colovesical fistula

Sir

I read with interest the paper by Rao and others (*Br J Surg* 1987; 74: 362–3) on the management of colovesical fistula, but note that treatment is not discussed—it is merely stated that radical excision of the sigmoid colon is the treatment of choice. Most of the patients I see with such fistulae due to diverticular disease present with 'benign' pneumaturia and minimal bladder involvement. I find it hard to recommend what is, in my hands at least, a life threatening operation to someone who is well and not inconvenienced. Is it the authors' knowledge of the outcome of the untreated disease that makes them recommend operation in all cases?

M. L. Crosfill

West Cornwall Hospital
Penzance
UK

Author's reply

Sir

We thank Mr Crosfill for his comments on our paper. Whilst it is reasonable to treat asymptomatic patients expectantly, it is our experience that the majority of patients have symptoms severe enough to justify major surgery.

P. N. Rao

Withington Hospital
Manchester
UK

Digital ischaemia in the lower limb

Sir

We read with interest the recent paper by Comerford *et al.* (*Br J Surg* 1987; 74: 493–5) detailing their experience of digital ischaemia in the lower limb secondary to embolization from proximal sites in the vascular tree.

To complement their survey of this clinical problem we would like to draw attention to the same problem in the upper limb which, although very much rarer, is potentially more serious should tissue loss result.

In the last 2 years we have treated three patients who presented with sudden onset of unilateral digital ischaemia with established digital gangrene in two cases. In each case an intracardiac source of emboli was ruled out by echocardiography. Arch aortography demonstrated a single plaque of atheroma in the first part of the subclavian artery in each case. There was no evidence of a thoracic outlet syndrome in any of these cases. Endarterectomy was felt to be the treatment of choice and was carried out either via a supraclavicular approach or via a median sternotomy with lateral extension, depending on the site of the plaque. Two of the patients required local digital amputations, but no further embolic episodes have been recorded with a mean follow-up of 6 months to 2 years. Pathological examination of the specimens demonstrated atheroma with superimposed recent thrombus.

Therefore, we would submit that unilateral ischaemia in the upper limb in the absence of an intracardiac source of emboli or a thoracic outlet syndrome should be investigated by early arch aortography. In our experience of this rare condition atheroma in the proximal subclavian artery appears to be the commonest site of origin of emboli.

A. J. Bryan
M. H. Lewis

East Glamorgan Hospital
Pontypridd
UK

Transcranial Doppler in asymptomatic occluded internal carotid artery

Sir

We read the paper by Dr Padayachee *et al.* (*Br J Surg* 1987; 74: 260–2) with great interest, since we believe that carotid compression tests are also valuable guidelines to surgical decision making in carotid surgery for asymptomatic patients. The surgical management of asymptomatic high-grade stenosis is still controversial[1,2]. However, we suggest that carotid endarterectomy is justified in patients with unilateral internal carotid artery occlusion, 'tight' or rapidly progressing carotid stenosis on the contralateral side and poor intra- and extracranial collateral circulation.

For example, a 67-year-old woman with hypertension was referred to our carotid Doppler laboratory in 1982 with bilateral, asymptomatic cervical bruits. Serial carotid Doppler studies indicated rapid progression of stenosis in both arteries. The transcranial Doppler (EME TC2-64) with carotid compression test was used to evaluate the collateral circulation and the results indicated that, in both cerebral hemispheres, blood supply depended largely on the left carotid artery in which stenosis was rapidly progressing. This was confirmed by digital subtraction arteriography. Therefore, we recommended a left carotid endarterectomy in order to avoid a catastrophic stroke.

Transcranial Doppler is a useful diagnostic tool in identifying a high risk subgroup of patients with asymptomatic carotid stenosis where carotid endarterectomy is justified.

N. M. Bornstein
A. Krajewski
J. W. Norris

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University of Toronto
Canada

1. Chambers BR, Norris JW. Outcome in patients with asymptomatic neck bruits. *N Engl J Med* 1986; **315**: 860–5.
2. Strandness DE. Outcome in patients with asymptomatic neck bruits. *N Engl J Med* 1987; **316**: 1088–9.

Breast abscesses

Sir

I was interested in the article by J. H. Scholefield *et al.* (*Br J Surg* 1987; **74**: 469–71). They offer no explanation as to why puerperal breast abscess is currently less common than sepsis associated with duct ectasia. I wonder if the Sheffield authors would care to speculate on possible reasons. I had wondered whether better hygiene, changes in breast feeding patterns and, perhaps, earlier treatment by the general practitioner with antibiotics all have a part to play, but I should be interested in the comments from Sheffield.

E. A. Benson

The General Infirmary
Leeds
UK

Sir

I am given to understand from the article by Scholefield *et al.* (*Br J Surg* 1987; **74**: 469–70) that all subareolar breast abscesses should be treated primarily by excision of the major duct system. I realize that mamillary fistulae following drainage of such abscesses is a common complication but will it not be more appropriate to treat these abscesses by drainage initially and do a definitive operation, such as the Hadfield's procedure, if the condition recurs?

K. Narayanan

Royal East Sussex Hospital
Hastings
UK

Authors' reply

Sir

We share Mr Benson's views on the possible factors leading to a reduction in hospital admissions due to puerperal breast abscess but would place greatest importance on the early use of antibiotics by the general practitioner.

Whilst we would certainly agree with Mr Narayanan that drainage of all established breast abscesses is necessary, whatever their site, it has been our clinical experience that the subareolar inflammatory mass usually contains very little pus and is best treated with appropriate antibiotics and recurrent problems dealt with by major duct excision.

K. Rogers
J. H. Scholefield
J. L. Duncan

Clinical Sciences Centre
Northern General Hospital
Sheffield
UK

Duodenogastric reflux after gastric surgery

Sir

We read with interest the article by Houghton *et al.* (*Br J Surg* 1987; **74**: 288–91) concerning the effects of duodenogastric reflux after gastric surgery.

A major weakness in this paper is the use of a chemical carcinogen (N-methyl-N′-nitrosoguanidine) to induce malignant change. It is now well established that operations which result in duodenogastric reflux in the rat will produce malignant change without the need to administer carcinogens[1,2]. In this study the incidence of malignant change in animals with duodenogastric reflux (Polya gastrectomy and total reflux groups) was 9 out of 58 (15·5 per cent) which is much lower than that reported by both Langhans *et al.*[1] (70 per cent) and our study[2] (58 per cent). In addition, the authors describe two adenocarcinomas in the control group which further confuses the interpretation of their data.

Finally the continued emphasis on bile as the cause of operation sequel carcinoma is at variance with our own experiments which were performed without the use of carcinogens[2]. These showed that pancreaticoduodenal secretions, and not bile, are implicated in the genesis of adenocarcinoma in the operated rat stomach when subjected to different components of duodenogastric reflux.

P. R. Taylor
P. H. Rowe
R. C. Mason
I. McColl

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1. Langhans P, Heger RA, Hohenstein J, Schlake W, Bunte H. Operational sequel carcinoma of the stomach. Experimental studies of surgical techniques with or without resection. *World J Surg* 1981; **5**: 595–605.
2. Mason RC. Duodenogastric reflux in rat gastric carcinogenesis. *Br J Surg* 1986; **73**: 801–3.

Placement of a permanent endo-oesophageal tube

Sir

The use of air insufflation and auscultation over the abdomen (*Br J Surg* 1987; **74**: 419) to assess the position of an endo-oesophageal tube is an ingenious but irrelevant solution to what is a non-existent problem for those using fibreoptic methods. Not only is fibreoptic endoscopy associated with a lower morbidity than rigid oesophagoscopy[1] but it carries the additional advantage of being able to visualize the whole length of the tube *in situ* by passing a thin (paediatric) endoscope through the lumen of the tube into the oesophagus or stomach beyond, thus enabling accurate positioning. Few specific indications for rigid oesophagoscopy remain and in our view blind pulsion intubation is not one of them. Surely the work of a centre dealing with one of the highest incidences of oesophageal carcinoma in the world would be eased by the adoption of fibreoptic methods for endo-oesophageal tube placement.

C. S. Robertson
M. Atkinson

University Hospital
Queen's Medical Centre
Nottingham
UK

1. Beachamp G, Duranceau AC. Diagnostic and therapeutic oesophagoscopy: indications, contraindications and complications. *Surg Clinics N Am* 1983; **63**: 807–13.

Book reviews

Gastrointestinal Oncology

J. Fielding and T. Priestman. 195 × 253 mm. Pp. 330. 1986. Tunbridge Wells: Castle House Publications Limited.

There are 29 contributors to this 300 page book of gastrointestinal oncology. The authors presumably espouse the idea of an organ specialist rather than a cell specialist. The book is divided into two parts.

The first part deals with general subjects including methods of treatment, aetiology, histopathology and screening tests. Curiously the methods of diagnosis are not discussed.

The second part consists of chapters running sequentially from gullet to anus plus chapters on lymphoma, smooth muscle tumours, carcinoid and endocrine tumours of the pancreas. The chapter content is rather uneven: no histological plates, radiographs or operative details are given in the majority of the chapters, but no less than ten histological slides are reproduced in the section on bile duct cancer (why don't they appear in the chapter on histopathology?). Radiographs of barium studies only appear in the small bowel section. Operative photographs (difficult to decipher) appear in the section on bile duct tumours. The reproduction of some of the radiographs is not good. The cholangiogram on page 167 is incomprehensible and the one on page 176 is back to front. There are no illustrations of diagnosis or surgical technique in the chapters on oesophagus, stomach, liver, large bowel or anus. The more uncommon tumours are well discussed. Each chapter is followed by a comprehensive reference list.

Perhaps the most spectacular development in gastrointestinal oncology in the last decade is in the treatment of anal cancer. It is now possible to cure the majority of patients without resorting to ablative surgery. Effective treatment in gastrointestinal oncology is otherwise limited to surgical excision with the possible exception of some patients with carcinoma of the oesophagus.

In summary, the state of the art is by and large well discussed in this volume and possible avenues of progress are pointed out.

J. Dawson

A Colour Atlas of Gynaecological Surgery. Volume 1. Vaginal Operations

D. H. Lees and A. Singer. 315 × 250 mm. Pp. 224. Illustrated. 1987. London: Wolfe Medical Publications Limited. £60.00.

It is always a great honour to be asked to review a new book; to review one which has been revised and moves into a new edition one has to be doubly careful, firstly, to examine the previous edition and identify the changes and secondly, to beware of criticism of a successful formula. With these caveats in mind I should first declare my position: I vastly prefer line drawings for explanation of surgical procedures. Only a well produced video is in my view superior.

This text is beautifully produced; all the photographs in the minor surgery section are clear and easily understood. However, in the major operation section many are very confusing and could only be interpreted by the experienced vaginal surgeon. It is a telling point that the major change between the first and revised edition has been the addition of explanatory line drawings and the use of overlaid lines and arrows on the photographs. In particular, the section on the Manchester repair remains as obscure as a rainy Manchester day.

It is also disappointing that some other procedures have not been added to what is a fairly small series of operations. The addition of new procedures would have allowed the introduction of the use of atraumatic sutures—surely trainee gynaecologists should not be encouraged in the use of eyed needles in the 1980s?

It is a pity that one or two editing errors spoil an otherwise beautifully produced first part of the book on minor procedures. The Sim's speculum referred to in the text under D&C is in fact an Auvard's in the photographs. The section on Laser evaporation for benign cervical lesions has clearly been lifted from the section on the treatment of CIN serving only to misguide the tiro.

To be successful any illustration of a surgical technique should be instantly recognizable: one should not have to refer to a series of numbers and lists to identify the basic structures. I have never seen a photographic atlas of surgery which has achieved this requirement; sadly this revised edition still falls short of this basic aim.

J. M. Monaghan

Clinical Paediatric Surgery. Third edition. Diagnosis and Management

P. G. Jones and A. A. Woodward. 235 × 155 mm. Pp. 574 + xiv. Illustrated. 1986. Oxford: Blackwell Scientific Publications. £25.00.

The third edition of this book by the staff of the Royal Children's Hospital, Melbourne, edited by Peter Jones and Alan Woodward, is to be welcomed. As in so many specialities, considerable advances have been made in paediatric surgery in the past 10 years—since the second edition. This is not a book for the practising surgeon but is certainly a good one for the house staff and students. It concentrates more on the clinical presentation and management of the surgical conditions affecting infants and children than on technical detail, and it demonstrates clearly and interestingly the wide spectrum of paediatric surgery. It is easy to read and will commend itself to those who like important points in the text stressed by italics.

It can be recommended as good initial reading in the subject for those approaching the surgical fellowship examinations and it will also prove useful to paediatricians preparing for the Diploma in Child Health, or the Membership examination in paediatrics.

If you wish to contribute to the children's ward library, or that in the casualty department, you can be sure that this book will be appreciated.

M. H. Gough

Surgical Infections

A. Pollock. 240 × 160 mm. Pp. 246 + x. 1986. London: Edward Arnold. £25.00.

Surgical infection is a topic which is always of interest to the surgeon, but one which most of us feel is not entirely within our intellectual grasp. There is something about infection which is frustrating for, with all the aids of sterility, antibiotics and good surgical technique, it should not be a problem, yet every honest surgeon finds it so. Alan Pollock with his established reputation in this field has tried to guide the surgeon through this maze but I had the feeling after reading the book that I could not be certain that I would always find the right path. The opening chapters on microbiology and immunology were superficial, and did not explore the subject in sufficient detail to make the reader confident of the scientific background to surgical infection. Similarly, the section on metabolic and haemodynamic consequences of sepsis goes so far, but does not increase the knowledge of the subject sufficiently to help in the practical management of the patient. The remaining sections are eminently practical, dealing with the audit of infection, acquired infections and postsurgical infections. In these parts there is something about everything but nothing in depth on some general surgical problems. This book serves as an introduction and as such should be read by all trainees in surgery. It whets the appetite for more, and this no doubt was the author's aim.

R. C. G. Russell

Modern Vascular Grafts

P. N. Sawyer. 235 × 155 mm. Pp. 326 + x. Illustrated. 1986. New York: McGraw-Hill. £135.

This is a useful book on vascular grafts. The history of the development of vascular grafts is particularly well referenced and it makes good reading. There are a number of good chapters explaining how most graft materials are not ideal for arterial replacement. Physical chemistry factors are discussed in detail with such important issues as electric charge on the inside of the graft and what effect this has on performance being highlighted. As well as a description of physical characteristics of vascular grafts, there are a number of chapters on specific grafts such as human umbilical vein and expanded polytetrafluoroethylene. The subject of endothelial cell seeding is topical and is covered well. All in all this is quite a useful book for a specialist but especially valuable to a surgeon who needs access to the vital references particularly on historical aspects of the development of graft requirements for arterial bypass.

R. M. Greenhalgh

Manual of Vascular Surgery. Volume 2

E. J. Wylie, R. J. Stoney, W. K. Ehrenfeld and D. J. Effeney. 310 × 230 mm. Pp. 338 + xvi. Illustrated in colour. 1986. Heidelberg: Springer Verlag. DM 590.

This is volume 2 of twin manuals on vascular surgery. Even those who are inured to the rise in cost of medical books in recent years will raise an eyebrow at this series. So what have we got for our money? Not a comprehensive textbook, neither do the authors attempt to present a balanced view of vascular surgery. Opinions and data, for example, are not supported by a bibliography. What we have is a superbly presented idiosyncratic account of the clinical policies and techniques of Dr Wylie, who sadly died in 1982, and his three eminent colleagues.

Particularly valuable is the extent to which this book deals with difficult and uncommon areas of vascular surgery, for example: complications of prosthetic grafts, non-atherosclerotic diseases of the carotid arteries, visceral artery compression syndromes, non-atherosclerotic renovascular hypertension, surgery of the inferior vena cava and the thoracic outlet syndrome. In the latter section it was interesting to read that the authors, having for some years used the axillary route for outlet decompression and first rib resection, have reverted to a supraclavicular approach which is very well described and illustrated. Some of us need all the help we can get in this testing area!

To say that this is an idiosyncratic account is no adverse criticism, for it confers a consistent approach and unequivocal guidance, as well as a welcome, slightly unorthodox flavour. A recurring theme, for example, is the use of autogenous artery grafts. These are harvested by substituting Dacron® graft for the lower aorta, and or iliac vessels, or by bench disobliteration of the occluded superficial femoral artery. These grafts are advocated for the replacement of the popliteal artery affected by adventitial cystic disease or aneurysm, femorofemoral cross-over, reconstruction of the renal artery, and replacement of the aneurysmal subclavian. It would have been nice, however, to have seen some data evaluating this type of reconstruction in comparison with conventional techniques.

There is a chapter entitled 'Amputation in the dysvascular patient'—ugh!—do the companion volumes, I wonder, deal with dysorthopaedic, dysgynaecological and dysneurological patients? The amputation techniques shown are fairly standard but there is an excellent description of the use of a rigid plaster dressing—a method whose merits do not seem to have been generally appreciated in the UK.

Refreshingly, at a time when most vascular literature puts a quite disproportionate weight on the benefits of the vascular laboratory, the emphasis is on clinical judgement. In the chapter on revascularization below the groin the only reference to the vascular laboratory is a mere two-sentence section devoted to segmental and ankle pressures. The chapter on amputation makes a little more concession to laboratory science, with several paragraphs dealing with the various methods used to determine the appropriate level of amputation, but the authors conclude that no technique can unfailingly predict the outcome of amputation and that the single most important determinant is surgical experience and judgement.

The most useful and striking aspect of this book is the depiction of surgical techniques beautifully illuminated by the artist Ted Bloodhart.

C. V. Ruckley

Gallstone Disease and its Management

M. C. Bateson. 240 × 160 mm. Pp. 244 + x. Illustrated. 1986. Lancaster: MTP Press Ltd. £42.50.

This multi-authored book aims to cover the subject of gallstone disease and has chapters on epidemiology, aetiology and natural history, as well as on diagnosis, medical and surgical management. I found the first three chapters on epidemiology, aetiology and natural history overlapped. The chapter on diagnosis was a good review of the techniques that have been, and are now used and was very well illustrated. The chapter on surgical management was, likewise, clear though three of the illustrations were generated by a word processor and lacked the quality expected in a printed volume and were out of style with other illustrations. The chapter on complications of surgery was clear and concise. Illustrations of the approach to the segment three duct were presented in the wrong sequence. The arteriogram and radiographs to illustrate haemobilia, later in the same chapter, were too faint. The chapters on endoscopic and oral medical therapy both gave up-to-date accounts of these subjects, and the book was concluded by a look towards the future by the editor. Overall, there is much to interest a physician or surgeon with an interest in gallstone disease.

R. W. Motson

Fluid Therapy in Childhood

T. L. Chambers. 214 × 137 mm. Pp. 140. 1986. Oxford: Blackwell Scientific Publications. £8.50.

This book is a joy to read and handles a complex subject with logic and clarity. The author, a paediatric nephrologist, recommends reading the book 'over a cup of coffee whilst waiting for laboratory results or watching an ill patient'. The style of this book makes it ideal for the busy resident doctor.

The first 60 pages give the physiological background, followed by 60 pages on 9 clinical topics, each chapter of a length to be read over one 'cup of coffee'! The topics are biased towards the needs of a medical paediatrician but the chapters on diabetes, kidney disease and metabolic conditions are relevant for a surgeon and the text includes surgical section headings for the reader short of time.

The management of the burn child is described by a plastic surgeon. It is unfortunate that a page has to be turned to read the formula for calculating colloid requirements in the first 24 h; this important information justifies a table as well as description in the text. The chapter on surgery is a well balanced review of management before, during and after an operation. It is curious that a surgeon was not invited to contribute especially as, in the preface, the author stresses the value of experience. In places, the units are not SI and conversion factors would have been helpful.

These are minor criticisms of a text which should be available on every children's ward; it is also highly recommended for senior clinicians to keep them up-to-date and for teaching purposes. The price is most reasonable. A second edition will certainly be required within a few years.

D. Drake

1986 Year Book of Digestive Diseases

N. J. Greenberger and F. G. Moody, 235 × 155 mm. Pp. 471. Illustrated. 1986. London: Wolfe Medical Publications Limited, £41.00.

The well-established Year Book series comprises 33 volumes (Anaesthesia to Vascular Surgery) providing a selected review of world literature from the preceding year. The 1985 volume for Digestive Diseases, published in September 1986, contains abstracts of 250 papers in gastro-enterology selected by the editors from a review of 80 journals. The papers reported have been accurately summarized and, where advantageous, original figures and tables have been included. Editorial comments which are usually pertinent and avoid patronizing the reader are appended to the abstracts.

It is not encyclopaedic, and is not for the specialist who is worried that he may have overlooked an out-of-the-way but crucial contribution to his field. Nor will it be a high priority for those who are working for the fellowship. Who then should read it? It is a good starting place for a talk at the weekly departmental meeting. I found it interesting to dip into, to find out what is happening in areas which I do not normally read about. It is best kept where it can be opened at odd moments to read an abstract or two—in the theatre coffee room while theatre sister decides if there are enough staff to do your case, or alongside the BMJs in the toilet. In the United States it has a more obvious market among those working for their Board of Speciality Review Exams, but in this country it will mainly be found in the medical library.

T. G. Allen-Mersh

Microvascular Perfusion and Transport in Health and Disease

P. F. McDonagh. 240 × 175 mm. Pp. 253. Illustrated. 1987. Basle: S Karger AG. £109.00.

This is not a book for surgeons. It could be a book for physiologists interested in the microcirculation but at £109 for just over 200 pages I doubt that many of them will be able to afford it. I have even greater doubt as to whether they should read it when I read that a certain Dr Flaim will give an 'over-view' of cardiac function and distribution of cardiac output but discover that of the 63 references at the end of the chapter the aforesaid Dr Flaim's name appears in 38.

When I discovered two of the few United Kingdom references with names wrongly spelt, it added to my general dissatisfaction with a book in which 11 people have summarized their last 5–20 years research. I would rather read the original papers than purchase this ridiculously overpriced book.

K. Burnand

Perioperative Assessment in Vascular Surgery

D. Preston Flanigan. 235 × 155 mm. Pp. 384 + xii. Illustrated. 1987. New York: Marcel Dekker Incorporated. $89.75.

My initial feeling on picking up this book was that here was yet another text book on vascular surgery that would add nothing to those already on my bookshelf. Having handled it and read through it, however, my view is that the Editor, Dr Flanigan has achieved yet another excellent little volume as part of the Science and Practice of Surgery series. As Dr Flanigan says in his preface, he had not intended the book to be an inclusive work on vascular diagnosis but it seems to me that, in 378 pages, 700 references and dozens of excellent diagrams and well reproduced X-rays, there is very little missing. The 27 American leading authorities on various investigative techniques have contributed in such a way as to enable the reader both to understand and undertake the procedures described. Summaries at the end of chapters are honest and reflective and the chapter on intra-operative carotid monitoring is an excellent example.

My quibbles with the book are minor. I cannot, for instance, accept that 'a common problem facing the vascular surgeon is ischaemia of the left colon after abdominal aortic reconstruction', in the chapter on assessment of bowel viability and, in the same chapter, no mention is made of tying the inferior mesenteric vein which might well contribute to this catastrophy.

Overall, I am impressed with the clarity of this book and the impression given that the authors have imparted their personal experience in a comprehensive manner. It is also a welcome sight to see British references appearing in what should become a reference volume on these invasive and non-invasive techniques.

C. A. C. Clyne

Notices and announcements

Meetings

31 August–4 September 1987
Surgical Efficiency and Economy
Lund, Sweden
Information: Professor S. Bengmark–SEE, Box 5121, S-220 05 Lund 5, Sweden

4–6 September 1987
IMLS. Quality Assurance Symposium
Liverpool, UK
Information: Mr D. Kilshaw, Department of Pathology, Arrowe Park Hospital, Arrowe Park Road, Upton, Wirral, Merseyside L49 5LN, UK

6–8 September 1987
An Introduction to Laser Surgery
Sheffield, UK
Information: Mrs V. M. Coomer, Regional Conference Centre, Lodge Moor Hospital, Sheffield S10 4LH, UK

9–11 September 1987
Clinical Controversies in Inflammatory Bowel Diseases
Bologna, Italy
Information: Organizing Secretariat, SO.GE.PA.CO. Spa. piazza Constituzione, 5/c, 40128, Bologna, Italy

14–18 September 1987
International Meeting on Tumour Necrosis Factor and Related Cytokinins
Heidelberg, FRG
Information: Professor H. Kirchner, Cancer Research Centre, Institute of Virus Research, Im Neuenheimer Feld, 6900 Heidelberg, FRG

15–18 September 1987
The British Society of Gastroenterology Jubilee Meeting
London, UK
Information: The Administrative Secretary, The British Society of Gastroenterology, 3 St Andrew's Place, Regent's Park, London NW1 4LB, UK

20–25 September 1987
32nd World Congress of Surgery
Sydney, Australia
Information: Secretariat, GPO Box 2609, Sydney, NSW Australia 2001

21–25 September 1987
Fourth ELMS Course in Biomedical Research Technique for Surgeons in Training
Southampton University Department of Surgery, UK
Information: ELMS, University Surgical Unit, General Hospital, Southampton SO1 6HU, UK

5th October 1987
An International Symposium of Second Generation Lithotripsy for Urologists and Hospital Administrators
London, UK
Information: Ms Pauline Sleight, BDI Conferences Ltd, Kensington Business Centre, 9–11 Kensington High Street, London W8 5NP, UK

11–16 October 1987
Annual Clinical Congress of the American College of Surgeons
San Francisco, California, USA
Information: American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-2797, USA

15–17 October 1987
Fourth Meeting of the European Chapter of the International Union of Angiology
Brussels, Belgium
Information: Madame D. Shanni, Administrative Secretariat, ECCO, Rue Vilain XIIII, 17a, B-1050 Brussels, Belgium

18–24 October 1987
Recent Advances in Pancreaticobiliary Surgery
Glasgow, UK
Information: Professor D. C. Carter, University Department of Surgery, Queen Elizabeth Building, Royal Infirmary, Glasgow G31 2ER, UK

22–23 October 1987
First British Symposium on Surgical Stapling
Manchester, UK
Information: Conference Coordinates, Confer House, 69 Kingston Road, New Malden, Surrey KT3 3PB

24–25 October 1987
Autumn '87 Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, c/o Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

1–6 November 1987
Progress in Cancer Management: Radiotherapy and Chemotherapy
London, UK
Information: Courses Department, The British Council, 65 Davies Street, London, W1Y 2AA, UK

5–6 November 1987
Annual Joint Scientific Meeting of the American Pancreatic Association and the Pancreas Cancer Section of the NCI Organ Systems Program
Chicago, Illinois, USA
Information: Midge Kellerhaus, American Pancreatic Association, Department of Surgery, M580, University of Missouri Medical Center, Columbia, MO 65212, USA

11–13 November 1987
First International Congress in Oral Cancer
Singapore
Information: Dr N. Ravindranathan, The Secretariat Department of Oral Surgery, Faculty of Dentistry, National University of Singapore, Kent Ridge, Singapore

15–18 November 1987
All Americas Health '87
Tampa, Florida, USA
Information: Denis Beckett, Fairs and Exhibition Ltd, 51 Doughty Street, Gray's Inn, London WC1N 2LB, UK

16–20 November 1987
Fourth International Symposium on Cardiorespiratory Emergencies
Rotterdam, The Netherlands
Information: Dr Omar Prakash, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands

1–2 December 1987
First International Symposium on Aids and the Surgeon
London, UK
Information: Ms Pauline Sleight, BDI Conferences Ltd, Kensington Business Centre, 9–11 Kensington High Street, London, W8 5NP, UK

23–24 January 1988
Hong Kong Surgical Forum Winter 1988
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

8–12 February 1988
Third Biennial Conference of the Indian Society of Oncology and the Indo–USSR International Workshop on Oesophageal Cancer
Bangalore, India
Information: Conference Secretariat: Kidwai Memorial Institute of Oncology, Hosur Road, Bangalore-560 029-India

5–7 May 1988
Biennial Congress of the European Council of Coloproctology 1988
Geneva, Switzerland
Information: General Secretary of the European Council of Coloproctology, Policlinique de Chirurgie, Hôpital Cantonal Universitaire de Genève, 1211 Geneva 4, Switzerland

Notices

Volunteers needed for 3–6 weeks surgical appointments in overseas Mission Hospitals. Please contact: Mr M. W. Flowers, Accident and Emergency, General Infirmary, Great George Street, Leeds LS1 3EX.

Leading article

Br. J. Surg. 1987, Vol. 74, October, 871–872

The specialty of hepatobiliary surgery

The Association of Surgeons has moved actively in recent years to strengthen its links with the surgeons of Europe. Lack of an agreed common language remains a problem and one particularly difficult barrier has been the mutual distrust British and French surgeons have for each others' alien tongue. At the same time, it has become increasingly clear that the French surgical literature contains much work of quality that surgeons in this country have been slow to comprehend. Nowhere has this been more evident than in the field of hepatobiliary surgery and the officers of the Association of Surgeons are to be congratulated on their choice of Professor Henri Bismuth of the Hôpital Paul Brousse as the Surgikos lecturer at the recent successful annual meeting in Liverpool. In a remarkable *tour de force* (delivered in English) Bismuth showed us just what can be achieved in this challenging field by application of sound anatomical knowledge, appropriate pre-operative and intra-operative assessment, and skilled surgical technique.

Much of the success of the Hôpital Paul Brousse programme is based on a thorough understanding of the surgical anatomy of the liver, and the debt to earlier workers, notably Couinaud[1], is freely acknowledged. According to the concept of functional hepatic anatomy, the right and left livers are separated by the main portal scissura, also known as Cantlie's line, which runs from the middle of the gallbladder bed anteriorly, to the left side of the vena cava posteriorly. The right and left livers are independent with respect to their portal and arterial blood supply, and the middle hepatic vein runs in the plane of Cantlie's line. Each liver can be divided into two sectors and further subdivision allows the description of eight segments[2]. Confusion between the French and Anglo-Saxon literature surrounds the use of the term lobectomy. According to Bismuth, resections may consist of hepatectomy (left or right), sectoriectomy or segmentectomy. In French eyes, right lobectomy consists of right hepatectomy extended to include removal of segment IV, the line of resection being the umbilical fissure.

In classical resection technique, preliminary vascular control can be achieved by first ligating and dividing the portal pedicle and hepatic vein before transecting the parenchyma. Alternatively, resection can be commenced by dividing the hepatic parenchyma with ligation of the hilar vessels and hepatic vein within the liver substance. Bismuth's preferred technique[2] combines elements of both approaches. For example, in right hepatectomy, hilar dissection first allows clamping of the portal and arterial elements without ligating them. The liver is then freed from the right side of the retrohepatic inferior vena cava. Dissection of the parenchyma then commences with ligation of the portal elements within the liver at the exact position required, the final ligation of the hepatic vein also being achieved within the liver. If indicated, as in right lobectomy for huge tumours, complete temporary vascular occlusion of the liver can be achieved by simultaneous clamping of the hepatic pedicle and occlusion of the inferior vena cava above and below the liver[3].

Intra-operative ultrasonography has been applied enthusiastically by Bismuth's group to supplement the information gained by pre-operative ultrasonography, CT scanning and selective arteriography[4]. In a review of 77 patients with primary liver tumours, intra-operative ultrasonography provided additional information in one-third of cases, modified the intended procedure in 21, and in 10 patients allowed subsegmental resection by facilitating guided cannulation and occlusion by balloon catheter of the branch of the portal vein supplying the part concerned. Intra-operative ultrasonography may have particular value in cirrhotic patients who develop hepatocellular carcinoma in that it may detect small tumours and also minimize the amount of liver that must be resected to eradicate them. While many of these technical advances in the use of intra-operative ultrasound have originated in Japan[5,6], their application in the West owes much to the French. In a recent review of 270 cirrhotic patients with hepatocellular cancer treated at the Hôpital Paul Brousse, 35 underwent liver resection ranging in extent from 'subsegmentectomy' to right hepatic lobectomy[7]. The operative mortality of 14 per cent is commendable in this group of patients but it remains to be seen whether favourable long-term results can be achieved in Western patients.

0007-1323/87/100871-02$3.00

Equally controversial is the use of hepatic resection for the treatment of hepatic metastases from colorectal cancer. In a series of 54 patients, hepatic resection has been achieved by Bismuth and his colleagues[8] without operative mortality, the extent of resection ranging from right hepatic lobectomy to segmentectomy and, in 14 cases, to 'metastasectomy'. While selection criteria have not yet been defined, the 1- and 3-year survival rates of 81 and 41 per cent respectively are tantalizing and, if such hepatic resection can be carried out without risk, consideration must be given to controlled studies.

This short review cannot adequately cover the other important contributions of Bismuth and his colleagues to hepatobiliary surgery. Notable contributions have been made to liver transplantation, with particular reference to emergency transplantation in fulminant hepatitis and to partial resection of liver grafts for orthotopic or heterotopic transplantation[9]. Useful contributions have been made to the management of liver injury[10] and to the challenging problem of iatrogenic bile duct stricture using the left branch approach[11] pioneered by Hepp and Couinaud[12]. Similarly, a thorough understanding of hepatic anatomy, now supplemented by intraoperative ultrasonography, has allowed the use of peripheral elements of the biliary tree for palliative bypass in patients with hilar cholangiocarcinoma[13].

This year's Surgikos lecture taught us a great deal about hepatobiliary surgery as a defined specialty. There is nothing mysterious about the success of Bismuth's programme. The basic pillars remain sound anatomy, appropriate pre- and intraoperative investigation and good surgical technique. The debt we owe to the French was recognized in the reception accorded to Bismuth; having reviewed the state of the art of liver surgery he came as close as could be imagined to the first standing ovation delivered by his normally undemonstrative British hosts.

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873–878

Anastomotic recurrence in large bowel cancer

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At the time of presentation approximately 60 per cent of patients with large bowel cancer are amenable to a 'curative' resection[1-4], that is complete removal of all macroscopic tumour. Of these potentially curable patients, 10–25 per cent will develop local recurrence[3-6], usually within 2 years of operation[7-8]. Anastomotic or suture-line recurrence is generally reported to develop in 5–15 per cent of patients[9-14], but the true incidence may be slightly higher. One study that included postoperative colonoscopy found an 18 per cent suture-line recurrence rate[15].

Pathogenesis of anastomotic recurrence

Potential mechanisms

Recurrent colorectal cancer involving the anastomosis may either be associated with extramural local recurrence or be confined to the suture line itself. When the anastomosis is involved in a tumour mass, it is often believed that the recurrence has started outside the bowel wall and spread inwards to reach the mucosal surface. Alternatively, a localized recurrence on the luminal aspect of the anastomosis might escape detection until large enough to present with associated extramural disease. Clinical data seldom allow a clear-cut differentiation between these two possible modes of spread.

Despite ostensibly complete removal of a tumour with favourable histological features, incomplete resection remains a possible cause of extramural recurrence involving the anastomosis. This view is supported, at least for rectal carcinoma, by two recent studies showing microscopic carcinoma deposits in the mesorectal lymphatics both distal to the tumour[16] and at the lateral excision margins[17]. Such tumour deposits, which are unlikely to be detected by routine histology, offer an obvious explanation for some unexpected local recurrences that involve the suture line.

It seems unlikely that recurrence confined to the anastomosis could be the result of incomplete resection. Satisfactory resection margins of intestine are easily achieved for intraperitoneal carcinomas and on the proximal aspect at least of rectal carcinomas. Theoretically, adequate rectal excision could be thwarted by the presence of tumour foci in the distal stump. Yet several studies have shown that distal intramural spread is uncommon and usually only affects a few millimetres of rectum[18-20]. Furthermore, there is no correlation between the extent of distal clearance of a rectal carcinoma and the incidence of local recurrence[21,22].

Alternative mechanisms for the development of anastomotic recurrence include implantation of exfoliated colorectal cancer cells and metachronous carcinogenesis at a site of proliferative instability. The traditional view that recurrence can result from implantation of exfoliated colorectal cancer cells[9-12,19,23-28] has recently been challenged[29]. The matter is of considerable practical importance. If cancer cells shed into the lumen can survive and grow elsewhere in the bowel or adjacent tissues, effective measures must be taken at operation to kill them. Metachronous carcinogenesis is a more recent concept which proposes that the suture line is a particularly fertile field for the development of tumour[30,31]. In the large bowel this hypothesis offers a likely explanation for anastomotic recurrence arising several years after primary resection. This review examines the evidence on which these two hypotheses are based.

Susceptible anastomoses

Anastomotic recurrence is more likely to develop at colocolic or colorectal anastomoses than at ileocolic anastomoses[10,12]. Wright[12] reported an overall 8·5 per cent incidence of suture-line recurrence in 838 patients after 'curative' resection of colorectal carcinoma. Tumours recurred at colocolic anastomoses in 12 per cent of cases and at ileocolic anastomoses in 0·7 per cent. The geographical distribution of suture-line recurrence within the large bowel could be explained by several factors. The direction of the faecal stream and the use of pre-operative enemas are likely to increase the desquamation of tumour cells in the left colon[32]; likewise, the greater manipulation involved in mobilizing distal colorectal tumours as opposed to proximal tumours. Yet exfoliated colorectal cancer cells have been found at each resection margin of right hemicolectomy specimens[33]. The relative rarity of both primary and (mucosal) secondary carcinoma in the ileum should certainly afford some protection to an ileocolic anastomosis[30]. In addition, the relative difficulty in diagnosing an ileocolic anastomotic tumour before it presents as a massive local recurrence may result in underestimation of the incidence of suture-line cancer at this site. Regular endoscopic surveillance would be necessary to determine the exact incidence of anastomotic recurrence at different sites within the large bowel.

Implantation metastasis

Evolution of the concept

In 1885 Gerster postulated that the mechanical dissemination of cancer cells at operation might lead to local recurrence of the tumour[34]. This suggestion attracted the support of several eminent surgeons during the next two decades while the foundations of cancer surgery were being established[35-37]. Careful biopsy techniques and *en bloc* resection were recommended, together with the use of cautery or 1 per cent formalin solution to kill liberated cancer cells and prevent implantation metastasis[36,38].

The probable seeding of exfoliated colorectal cancer cells on to raw bowel mucosa was described by Mayo in 1913[39]. He reported a patient who developed a nodule of carcinoma at the mucocutaneous junction of a colostomy 7 weeks after resection of a rectal cancer. As anterior restorative resection for distal large bowel cancer gained popularity in the 1930s, there were increasing reports of recurrence involving the anastomosis[9-12,32]. Gordon-Watson in 1938 suggested that free cancer cells could be implanted into the bowel wall by the needle during suturing or might grow directly on the raw anastomosis[40]. General acceptance of this view prompted the use of various operative measures designed to kill these cells or limit their dissemination[9,27,41-43]. Irrigation of the bowel lumen with cytotoxic agents, usually mercuric perchloride or sodium hypochlorite, and isolation of the tumour with tapes before mobilization became established practice in colorectal surgery.

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The early evidence in support of implantation recurrence at the suture line was persuasive but not entirely conclusive. It relied heavily on clinicopathological studies of patients who developed local recurrence. Wheelock and his colleagues followed 90 patients who had undergone curative resection for distal carcinomas resulting in an anastomosis within 15 cm of the anus[11]. Excluding patients with pelvic recurrence or peritoneal seedlings, ten cases of suture-line recurrence were observed on sigmoidoscopy. In eight of these cases the primary tumour was Dukes' A, and in nine primary resection specimens there was at least 3·5 cm of normal bowel distal to the tumour. The authors therefore reasonably suggested that implantation was more likely to be the cause of recurrence at the anastomosis than incomplete resection. Identical conclusions were drawn from a study by Lofgren and co-workers, in which 86 of 108 local recurrences following anterior resection involved the suture line[25]. After gross and microscopic examination of 98 original specimens and 27 subsequent specimens, 76 recurrences could not be explained on the basis of either incomplete resection or lymphatic and vascular permeation. Similar results from St. Mark's Hospital[23] and New Orleans[32] supported the view that some anastomotic recurrences were the result of implantation of exfoliated cancer cells.

Clinical evidence

Numerous case reports of carcinoma deposits arising downstream from a colonic or upper rectal tumour suggest that exfoliated colorectal cancer cells are capable of implantation. Tumour deposits on raw mucosal surfaces such as haemorrhoidectomy wounds, anal fissures and fistulas have often been described[19,44-48]. We have recently experienced such a case (*Figure 1*). In this patient, as in many others[19,44-48], direct seeding of free cancer cells appears the most likely explanation for the development of recurrence.

Possibly the most compelling clinical evidence for implantation was the observed reduction in the incidence of suture-line recurrence following the introduction of measures to kill or limit the dissemination of desquamated cancer cells[27,42,43]. Before these measures were adopted the reported incidence of suture-line recurrence ranged from 8·5 to 36·0 per cent[9-12,27,32]. At St. Mark's Hospital, for example, the routine use of 0·2 per cent mercuric perchloride for bowel lavage reduced the incidence of anastomotic recurrence from 13 per cent to less than 3 per cent[27]. Similarly, in Chicago the use of occlusive tapes to isolate the tumour before mobilization plus bowel lavage with 0·25 per cent sodium hypochlorite completely prevented suture-line recurrence in 101 patients followed for at least 1 year[43]; previously the same surgeons had had a 10 per cent incidence of anastomotic recurrence[9]. In interpreting these results we should not overlook the possibility that heightened awareness of the problem and a general sharpening of surgical technique as a consequence may have contributed to the improvement.

Other studies provide circumstantial evidence to support the role of implantation of exfoliated carcinoma cells in the development of anastomotic recurrence. Bader and Papanicolaou sought exfoliated malignant cells to establish the original diagnosis of colorectal carcinoma[49]. Oakland used colonic exfoliation cytology to confirm or refute the diagnosis of cancer in 97 patients with equivocal endoscopic and radiological findings: of 24 patients eventually found to have a carcinoma, 18 were first diagnosed by colonic cytology[50]. Likewise, Rosenberg has also found colonic exfoliative cytology a useful diagnostic tool[51]. Dissemination of exfoliated cancer cells along the bowel was studied by McGrew[52]. In 50 tumour-bearing specimens malignant cells were found proximal to the tumour in 42 per cent at a mean distance of 21 cm and distal to the tumour in 65 per cent at a mean distance of 10 cm. Half the specimens yielded cancer cells at least 10–15 cm away from the tumour. In one case they were retrieved 35 cm away and in another proximal to the ileocaecal valve. Although these workers found that occlusive ligatures limited the dissemination of cancer cells, others have not[53].

Experimental evidence

Animal studies using a variety of tumour cells, both animal and human, have confirmed that malignant cells are capable of implanting and giving rise to metastases at a suture line[54-58]. Transection and re-anastomosis of rabbit colon in the presence of cells from the Browne-Pearce (rabbit) testicular tumour resulted in anastomotic and peritoneal deposits[54,55]. Protecting the suture line from tumour cells until after completion of the anastomosis did not prevent these deposits[59]. Suture material passed through a solid tumour or a suspension of malignant cells can result in transferral of cells and implantation metastasis in recipient animals[60].

These findings prompted the use of iodized catgut sutures, which were shown to be effective in preventing implantation in the animal model[61-64] but have not been generally adopted in clinical practice. Cohn and his colleagues showed that Browne-Pearce tumour cells would not grow on a mucosal surface, but they could produce anastomotic tumours by seeding on to the serosal surface of the bowel or into the bowel wall via the suture material[65,66]. Thus an anastomotic recurrence associated with extraluminal tumour does not necessarily reflect invasion inwards of an extramural focus of cancer left behind by

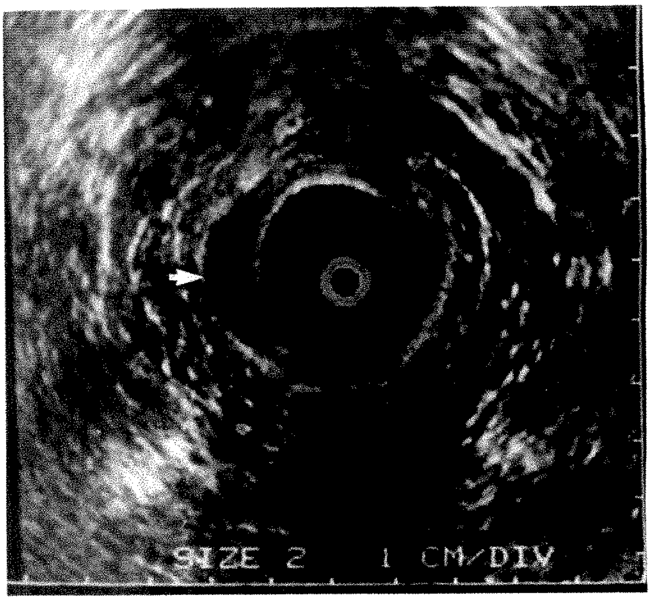

Figure 1 *Endoluminal ultrasonography of the rectum showing an implantation metastasis (arrowed) at the site of excision of a benign adenoma. The tumour has breached the submucosa but not the muscularis propria. Six months earlier the patient had undergone peranal local excision of a tubulovillous adenoma followed by a low anterior resection of a Dukes' B rectal carcinoma. Abdominoperineal excision of the rectum was undertaken and histology of the specimen confirmed a Dukes' A carcinoma with no extension to the previous anastomosis (illustration kindly provided by Mr John Beynon FRCS)*

incomplete resection. Animal experiments also confirmed the clinical experience that suture-line recurrence is commoner at a colocolic anastomosis than an ileocolic anastomosis[67].

Recent conflict

The hypothesis of implantation metastasis was seriously challenged in 1978 by Rosenberg *et al.*[29], who investigated the viability of human intraluminal cancer cells for the first time. Exfoliated cells were retrieved by pre-operative colonic lavage in 10 patients and by lavage of the opened tumour-bearing resection specimen in a further 27 patients. Viability was determined by several means: exclusion of the supravital stain trypan blue, non-specific esterase activity, tritiated thymidine uptake and tissue culture capability. In 25 cases cell suspensions of the solid carcinoma were also examined. No exfoliated tumour cells obtained by colonic lavage of the intact or resected intestine were viable by any one of these tests, whereas approximately half the solid tumour suspensions contained viable cells. The authors concluded that exfoliated cells were an unlikely cause of recurrent cancer of the large bowel.

Our own work directly contradicts Rosenberg's findings and resuscitates the concept of potential implantation. We have found millions of viable exfoliated cancer cells in the bowel lumen adjacent to the sites of transection in the excised specimen[33]. These cells were obtained both by pre-operative colorectal lavage and by irrigation of the proximal and distal sites of transection in the excised specimen. We used a density centrifugation column to concentrate the tumour cells and confirmed their viability by both trypan blue exclusion and hydrolysis of fluoroscein diacetate. Viable cells were obtained in large numbers in 74 per cent of lavage specimens and 69 per cent of resection margins, whether proximal or distal.

Tumour cells could be viable yet incapable of proliferation and thus unable to produce a metastasis. We therefore investigated the proliferative and metastatic potential of tumour cells retrieved by luminal lavage by testing their ability to incorporate tritiated thymidine and grow as xenotransplants in T-cell depleted mice. Tumour cells from seven of twelve patients incorporated tritiated thymidine as demonstrated by autoradiography. Of 17 tumour cell suspensions injected into the tail vein of 5-month old immune-deprived mice, 6 resulted in solid pulmonary carcinoma nodules[68]. In support, tissue culture growth of intraluminal exfoliated colorectal cancer cells has recently been reported[69].

Besides cancer cells being shed into the lumen of the bowel, free cancer cells have also been found on the serosal surface of large bowel tumours, in peritoneal fluid (in the absence of peritoneal metastases)[69–72] and in the mesorectum[69]. If free cancer cells are capable of implanting at the anastomosis, then it is likely that implantation can also occur on other raw areas, including the tumour bed. Thus extraluminal local recurrence could also be the result of implantation.

Prevention of implantation metastasis

The evidence presented strongly supports the likelihood of implantation of exfoliated cancer cells as a cause of anastomotic recurrence in large bowel cancer. Several measures have been undertaken at operation both to kill exfoliated cancer cells and to limit their dissemination. Cole advocated the use of occlusive tapes placed proximal and distal to the cancer before manipulation[9,41]. Although he showed no cancer cells outside the isolated segment of tumour-bearing bowel[52], others found this method ineffective both clinically[32] and experimentally[53,73].

Many clinical studies support the efficacy of irrigating the transected bowel ends with cytotoxic agents before fashioning an anastomosis[27,42,43]. Mercuric perchloride 1:500 has been used extensively in this country with clinical benefit[27], although systemic toxicity and even death have complicated its use in clinical practice[74,75]. Other agents routinely used include chlorhexidine-cetrimide, sterile water and aqueous povidone-iodine[76]. Cytotoxicity testing *in vitro* has shown chlorhexidine-cetrimide and povidone-iodine at 5 per cent concentration to be rapidly lethal to carcinoma cells, whereas sterile water is unreliable[76]. We therefore recommend routinely cleansing the bowel ends with either chlorhexidine-cetrimide or povidone-iodine before creating the anastomosis. During anterior resection of the rectum a clamp is placed across the bowel below the tumour and the distal rectal stump is irrigated through a large catheter passed *per anum*.

The role of adjuvant pelvic radiotherapy in the management of operable rectal cancer is still being evaluated[77]. The rationale for pre-operative radiotherapy is to decrease the number of viable tumour cells and thus to reduce the incidence of local and distant recurrences arising from incomplete resection or operative dissemination of cancer cells. Postoperative radiotherapy should 'sterilize' any residual malignant tissue including exfoliated cancer cells. The results of trials employing pre-operative radiotherapy have recently been reviewed by Cummings[77]. Low-dose pre-operative irradiation regimes (up to 2500 cGy) have not shown a major benefit in terms of either reduced local recurrence or improved survival[78–80]. Uncontrolled studies and early trial reports indicate that high-dose pre-operative radiotherapy may be effective in reducing pelvic recurrence[81,82]; these data require confirmation. Pre-operative radiotherapy can exert a biological effect on the primary tumour in terms of diminished size and fewer involved lymph nodes[78].

The effect of postoperative irradiation has been the subject of fewer trials. The advantage of this regime is that histopathological staging is accurate and healing already complete. Therefore patients with Dukes' A carcinoma, who are unlikely to benefit from radiotherapy, can be excluded, as can patients with disseminated disease who may benefit more from alternative adjuvant therapies. The major disadvantage is the increased risk of irradiating small bowel and other viscera displaced by operation. The recent trial by the Gastrointestinal Tumor Study Group demonstrated only a modest benefit both in terms of pelvic recurrence and survival[83]. The lowest incidence of pelvic recurrence was seen in patients receiving a combination of radiotherapy and chemotherapy, but survival was not significantly improved.

Metachronous carcinogenesis

Clinical evidence

Although no direct clinical evidence exists to support this hypothesis there are cogent theoretical arguments. The field of growth concept for the development of neoplasia is widely accepted[84]. The occurrence of multiple adenomas and carcinomas supports the view that epithelial neoplasia of the large bowel is a multifocal disease. In the large bowel adenomas are multiple in 28–35 per cent of patients at the time of diagnosis[85,86], and carcinomas are multiple in 3–5 per cent, whether synchronous or metachronous[85,87]. Moreover, the presence of synchronous adenomas at the time of resection for carcinoma doubles the risk of developing a metachronous large bowel cancer[88]. The strong association of familial polyposis coli and longstanding ulcerative proctocolitis with the development of carcinoma also supports the concept of an unstable epithelium[85,89]. In this 'primed situation' we believe that the anastomosis could provide a particularly fertile field for the development of a metachronous carcinoma and that adaptive hyperplasia of the epithelium at the suture line may have an important role[30,31]. Approximately 30 per cent of recurrences at the suture line arise 2 years or more after primary resection for large bowel cancer (*Figure 2*). In these cases metachronous carcinogenesis offers a more plausible explanation of recurrence than either implantation of cancer cells or incomplete resection.

Experimental evidence

Consistent with the 'field of change' concept are the differences in goblet cell mucins found at varying distances from a

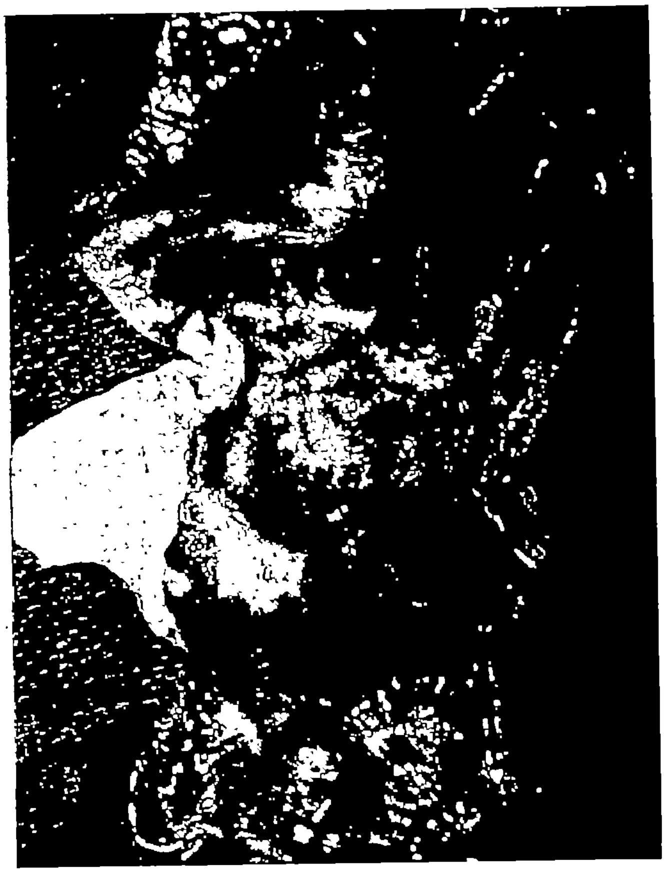

Figure 2 *Metachronous carcinogenesis. Adenocarcinoma of the colon arising at the colorectal anastomosis in a man of 70 years who had undergone sigmoid colectomy for Dukes' B carcinoma 14 years earlier*

carcinoma. Filipe describes a transitional mucosa adjacent to carcinomas in which there is an increase in the normal sialomucin to sulphomucin ratio[90,91]. Of clinical relevance is the markedly increased incidence of recurrence at the suture line when anastomoses are fashioned with transitional mucosa[92,93]. Recent experimental studies using Sprague–Dawley rats have indicated that this difference in goblet cell mucins may simply be a feature of an immature mucosa, i.e. local intestinal hyperplasia[94].

Intestinal resection performed at different levels of the small and large bowel in rats pretreated with azoxymethane results in a striking propensity for neoplasms to develop at, or immediately adjacent to, the sites of anastomosis[30,31,95–99]. As tumours develop preferentially at the suture line even when operation precedes carcinogen[30,31], implantation of transformed cells shed at operation cannot be the explanation in this model. For anastomotic tumours to develop, at least one of the involved bowel ends must be vulnerable to the carcinogen. Thus an ileo-ileal or ileocaecal anastomosis is relatively immune, whereas duodenal, colocolic and colorectal anastomoses are often affected[31,97]. Azoxymethane favours the distal colorectum and proximal small bowel rather than the ileocaecal region[95–97].

We have recently studied the relationship between the proliferative status of the mucosa and the susceptibility of an anastomosis to tumour development[100]. Azoxymethane was administered to Sprague–Dawley rats at varying intervals from 0 to 12 weeks after transection of the mid-descending colon. Colonic anastomoses displayed increased susceptibility to tumour development for up to 3 months after their creation. Throughout this period cell proliferation was increased in the immediate vicinity of the anastomosis, as shown by thymidine-labelled autoradiography and morphometry. These findings support the hypothesis that hyperplasia predisposes to neoplasia in the intestinal tract[97].

Outcome of patients with anastomotic recurrence

Local recurrence of large bowel cancer is associated with substantial morbidity and mortality rates. Surgical reresection offers the only real chance of cure in patients with recurrent colorectal cancer. 'Curative' reresection rates for local recurrence range from 2 to 14 per cent in most series[8,101–104]. More encouraging results have been reported recently from a prospective follow-up study[105], which involved regular endoscopy. By this means 41 per cent of local recurrences were diagnosed. An overall 'curative' reresection rate of 40 per cent was achieved. Similar results have been reported for the treatment of anastomotic recurrence[106]. Regular postoperative endoscopy is therefore worthwhile and may enable the early diagnosis of local recurrence, notably at the anastomosis, at a time when curative reresection is possible.

In conclusion, many cases of anastomotic recurrence cannot be ascribed to incomplete resection of primary carcinoma. Alternative mechanisms of recurrence include implantation of exfoliated colorectal cancer cells liberated at the time of operation and metachronous carcinogenesis. Implantation is more likely to result in the development of 'early' recurrence at the suture line, whereas metachronous carcinogenesis provides a likely explanation for the development of 'late' recurrence. Meticulous technique including the use of measures to prevent implantation metastasis should minimize the former; prolonged surveillance is required to detect the latter.

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Paper accepted 3 June 1987

Announcement

A seminar will be held at 2.00 p.m. on Wednesday, 18 November at the Royal College of Surgeons to consider the potential for personnel selection techniques and aptitude testing as an aid to the selection of surgical trainees. Speakers will include a member of a firm of management consultants, the Commandant of the Royal Air Force Officer and Aircrew Selection Board, and the Director of the personnel selection firm which is advising The Netherlands' Association of Surgeons in a scheme they have recently adopted for this purpose.

Association of Surgeons of Great Britain and Ireland

Br. J. Surg. 1987, Vol. 74, October, 879–883

A meeting of the Association of Surgeons of Great Britain and Ireland took place in Liverpool on 1–3 April 1987. The President of the Association, Professor Robert Shields, was in the chair.

The Moynihan Prize was awarded to P. McCulloch and W. D. George for their paper 'Warfarin inhibition of metastasis: the role of anticoagulation'.

Warfarin inhibition of metastasis: the role of anticoagulation

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Warfarin inhibits metastasis in animal models by mechanisms that remain unclear. A better understanding of this phenomenon may clarify processes underlying metastasis in human cancer. We have studied the effects of warfarin on metastasis in a rat model by intravenous injection of Mtln3 mammary carcinoma cells and subsequent counting of pulmonary seedlings. To determine whether warfarin acts principally on the tumour cell or the host, we pretreated either cells or animals with warfarin before intravenous injection of 10^4 Mtln3 cells. Pretreatment of tumour cells had no effect, whilst pretreatment of the host reduced median seedlings from 67 to 4·5 per animal ($P<0{\cdot}005$). *To determine whether warfarin was acting via its anticoagulant action, we reversed warfarin anticoagulation by intravenous injection of coagulation factors II, VII, IX and X. Restoration of coagulation for 12 h immediately after injection of cells completely reversed the warfarin effect* ($P<0{\cdot}001$), *but if the injection of factors was delayed for 12 h it had no effect* ($P=0{\cdot}1753$). *We conclude that warfarin acts principally on the host, not the tumour cell, and that it acts via its effect on coagulation. The restriction of the effect to the first 12 h after tumour cell injection suggests a mechanism involving intravascular processes such as tumour cell survival or endothelial adhesion.*

Keywords: Metastasis, anticoagulants, warfarin

Metastatic dissemination of cancer via the bloodstream is the most important obstacle to the effective treatment of malignant disease, and the ultimate cause of death in the majority of patients. The mechanism of this phenomenon remains unclear because of its great complexity and the many possible influences upon it. Current theories[1,2] view metastasis as a multistep process in which successive obstacles are overcome by a small sub-population of tumour cells capable of doing so. Each step requires different properties, and is susceptible to different influences, and each step in turn influences those subsequent to it. It is therefore necessary to break the process down into smaller components for the purposes of study. This can be achieved by studying influences which increase or decrease metastasis, and attempting to define the point in the process at which they have their effect.

The anticoagulant drug warfarin is an example of such an influence. Warfarin markedly inhibits metastasis in a number of animal models[3–7], but whether this effect is due to its anticoagulant properties remains uncertain. There is an extensive literature documenting the coagulation disturbances in cancer[8–12], and suggestive evidence of a role for coagulation in the spread and growth of tumours[10,13,14]. On the other hand Hilgard and Maat[5] have reported that the warfarin effect can be abolished by administering vitamin K, but not by giving factor concentrates which restore coagulation to normal, and Colucci *et al.*[15] showed that warfarin treatment of tumour-bearing animals reduces the capacity of the tumour cells to produce a procoagulant substance, as well as their metastatic potential. These studies suggest that the activity of warfarin might be mediated by an alteration in the metabolic activity of the tumour cells rather than that of the host. Other hypotheses have been put forward based on observations of decreased tumour cell motility in the presence of warfarin[16] and of interactions between warfarin and macrophage function[17]. The possibility that warfarin acts as a cytotoxic agent has been investigated in several different models[4,18–20] with diverse results. The principal means by which warfarin reduces metastasis therefore remains undefined. We believed that an investigation of this subject might provide valuable insights into the mechanism of the metastatic process, having possible relevance to the clinical situation. We have therefore developed an animal model of metastasis in the Fischer 344 rat, and have used this to study the means by which warfarin anticoagulation inhibits metastasis. We have addressed first the question of whether warfarin acts principally on the tumour cells or the host animal, and secondly the mechanism by which its action upon the host occurs.

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Materials and methods

Metastatic tumour model

The animals used in this study were female Fischer F344 inbred rats between 6 and 8 weeks old (Olac Limited, Bicester, UK). The average weight at the time of use was 130 g. Animals were housed four to a cage and fed normal rat diet. No measures were taken to avoid coprophagy.

The tumour used was the Mtln3 clone of the spontaneously metastatic rat mammary carcinoma 13762NF. Cells were kindly donated by Drs Neri and Nicolson of the MD Anderson Hospital and Tumour Institute, Houston, Texas, the originators of the clone[21]. Cells were cultured in 75 cm^2 tissue culture flasks (Nunc/Intermed, Kamstrup, Denmark) in equal parts of Hams' F10 and Dulbecco's Modified Eagle's Medium (F10/DMEM), with 10 per cent fetal calf serum (FCS) but without antibiotics. Cultures were maintained at 37°C in equilibrium with 2 per cent carbon dixoide in air. Cells were passaged a maximum of six times between thawing and use, to minimize problems of phenotypic drift[22].

Animals were inoculated with tumour cells in F10/DMEM by either the intravenous or the subcutaneous route, as required for different experiments. Following preliminary experiments a dose of 10^6 cells in 0·2 ml of F10/DMEM was adopted for subcutaneous inoculation, and one of 10^4 cells in the same volume for the intravenous route.

Lung metastases were detected by the method of Wexler[23]. Briefly, this involves excising the lungs from the animal and inflating them via the trachea with a carbon black solution. The preparation is then bleached for 48 h in Fekete's solution, revealing surface pulmonary metastases as white nodules. Conventional histology confirmed the accuracy of this method for detection of tumour deposits: multiple deposits were noted histologically in sections from all lungs found positive by Wexler's method, whilst no false positive identifications of metastasis were made. Full autopsy was carried out on all animals killed, and samples of any tissue suspected of containing metastases was submitted for histological examination.

Anticoagulation

As noted by previous authors[7], maintenance of a steady level of anticoagulation in the rat using warfarin is difficult, and requires frequent measurement of the effect with *ad hoc* adjustment of the dose. After several pilot studies, the following procedure was adopted. Warfarin was administered in the drinking water at a concentration of 2 mg/l for 48 h, then at 1 mg/l for 24 h. Thrombotest (Nyegaard, Oslo) estimations were then performed on one rat from each cage, using 50 μl of free flowing blood. Dose adjustments were aimed at maintaining the Thrombotest within the range 68–170 s (16–4 per cent of rat normal activity). No tumour experiment was begun until the median Thrombotest result had been within this range for 24 h. Warfarin treatment was continued for 24 h after the intravenous injection of tumour cells, and the Thrombotest was monitored every second day until it had returned to normal. This method of warfarin treatment produced no mortality when used in short-term studies. Warfarin was given continuously until sacrifice to animals receiving subcutaneous tumour implants. This form of treatment carried a 10–15 per cent mortality from haemorrhage, whatever monitoring system was employed.

Effect of warfarin on spontaneous metastasis

To determine the effect of warfarin treatment on spontaneous metastasis from an implanted tumour, two groups of 15 rats were inoculated subcutaneously with 10^6 Mtln3 cells. One group received no treatment; the other received oral warfarin as detailed above. Animals were killed at 23 days: the weight of the primary tumour was recorded, and metastases estimated by the method of Wexler.

The site of action of warfarin

This experiment was designed to determine whether warfarin inhibits metastasis principally by affecting the host or by acting on the tumour cells. Three groups of 15 rats were used. All received tail vein injections of 10^4 Mtln3 cells in 0·2 ml of F10/DMEM with 10 per cent FCS. Group A animals were anticoagulated with warfarin before the injection of tumour cells. Group B animals received no warfarin, but the cells with which they were inoculated were pre-incubated for 3 days in medium containing a 10 μmol/l concentration of warfarin. Group C acted as controls, receiving no warfarin and being injected with untreated cells. Thrombotest was monitored daily until it had returned to normal in all groups. Animals were killed at 17 days after injection, and lung tumour formation estimated by the method of Wexler.

The effect of reconstituting coagulation

The following experiment was performed to determine the nature of any effect of warfarin on the host animal. The two points considered were: whether the effect was mediated via the coagulation system or by some other effect on the host; and which parts of the metastatic sequence might be influenced by a coagulation-mediated effect. A heat-treated concentrate of human Factors II, IX and X was kindly donated by Dr R. J. Perry of the Protein Fractionation Centre, Edinburgh, and a heat-treated concentrate of human Factor VII by Dr J. K. Smith of the Protein Fractionation Centre, Churchill Hospital, Oxford, UK. These were used in preliminary experiments to determine the dose required to reconstitute coagulation in the fully warfarinized rat. For the purposes of the experiment each rat was given a dose representing 6 units of Factors II and X, 7 units of Factor IX and 10 units of Factor VII. One unit is sufficient to restore 1 ml of completely depleted human plasma to normal activity for the factor concerned. The dose was repeated after 6 h, with the aim of maintaining normal coagulation continuously for 12 h.

Four experimental groups were employed:

Group 1 were not warfarin treated and received untreated tumour cells;

Group 2 were fully warfarinized before receiving tumour cells IV; these animals received no reconstitution treatment;

Group 3 were fully warfarinized before receiving tumour cells IV; reconstitution treatment was started immediately after tumour cell injection;

Group 4 were fully warfarinized before receiving tumour cells IV; reconstitution treatment was started 12 h after tumour cell injection.

Groups 1, 3 and 4 contained 12 animals each; Group 2 contained 6 animals (*Figure 1*). All animals received 10^4 Mtln3 cells IV and were killed and examined on day 17 as described above.

Statistical analysis

Mean tumour weights were compared using an unpaired *t* test. Comparison between groups for numbers of lung metastases was by Mann–Whitney *U* test.

Results

Anticoagulation

The regimen described successfully maintained mean Thrombotest time within the target range (mean 101 s) with an acceptably small degree of variability (s.e.m. 14·3 s). Mean warfarin concentration measured in plasma at the time of tumour cell injection was 1·63 μmol/l.

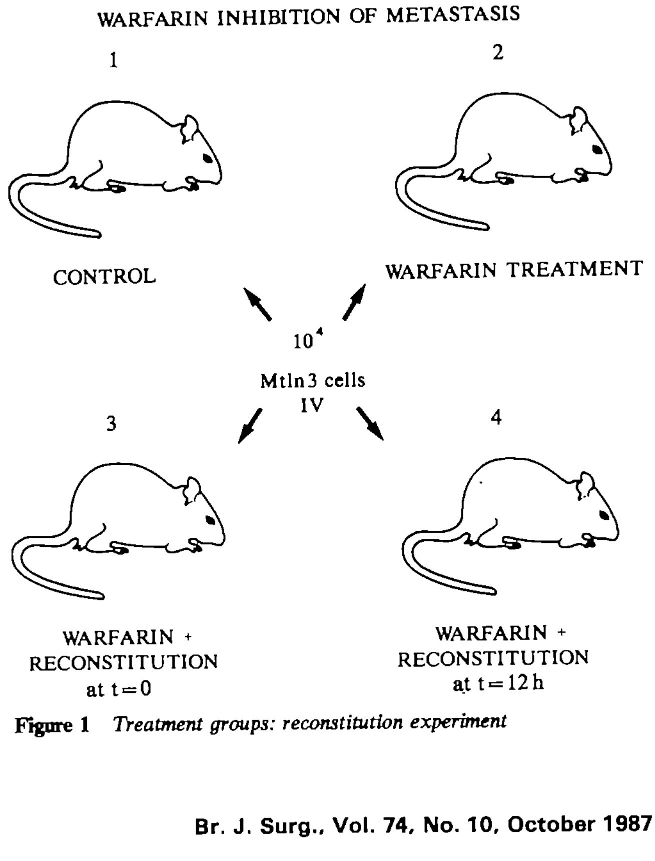

Figure 1 *Treatment groups: reconstitution experiment*

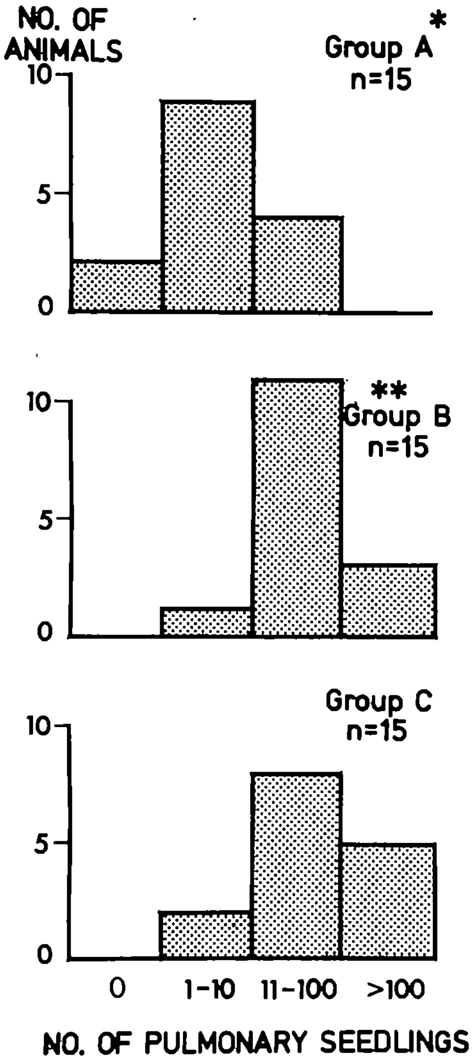

Figure 2 *Pulmonary metastases after warfarin treatment of tumour or host. Group A, animals warfarin treated; Group B, cells warfarin treated; Group C, control animals.* **A* versus *C*, $P<0{\cdot}005$ *(Mann–Whitney)*, ***B* versus *C*, $P>0{\cdot}1$ *(Mann–Whitney)*

Warfarin and metastasis from implanted tumours

Three animals in the warfarin treatment group and one in the control group died before the planned date of death, and could not therefore be included in the analysis. The three treated animals all died from haemorrhage, as confirmed by autopsy: the cause of the other death was not identified. These results were consistent with our previous experience with this model. All surviving animals in both groups remained in good condition until 4 days before death, when they began to lose weight due to the effects of their advancing tumours. Continuous warfarin treatment had no discernible effect on the size of the primary tumour which developed after inoculation of Mtln3 cells subcutaneously. The mean tumour weight was 12·03±1·61 g for warfarin-treated rats and 11·38±1·71 g for controls. There was, however, a significant reduction in pulmonary metastases in the treated animals. A total of 7 of 12 treated rats were free of pulmonary metastases, as compared with 3 of 14 in the control group. Warfarin-treated animals that developed metastases had fewer lesions than controls; the median number of metastases was 8 in the untreated animals (range 0–133) whilst in the warfarin-treated animals the median number was 0 and the range 0–21. This difference was statistically significant ($P<0{\cdot}05$, Mann–Whitney). Metastases to regional and mediastinal lymph nodes were commonly found in both groups, but no metastases to other viscera were detected.

Tumour versus *host effects*

Administration of oral warfarin inhibited seeding from intravenously injected tumour cells by over 90 per cent compared with controls (*Figure 2*): the median number of metastases in warfarin-treated animals (Group A) was four, whilst in untreated controls receiving untreated cells (Group C) it was 67 ($P<0{\cdot}005$, Mann–Whitney). Administration of warfarin to the tumour cells before injecting them, on the other hand, seemed to have no effect on the metastatic rate. The median number of metastases in this group was 54, and the distribution of results similar to that in Group C.

Anticoagulant versus *other effects*

The aim of the next experiment was to reconstitute the coagulation system of a fully warfarinized animal, and note whether this abolished the antimetastatic effect. In a preliminary experiment the complex of human coagulation factors used was successful in reducing the Thrombotest time of a group of treated rats to near-normal values for up to 12 h (*Table 1*). The mean value after 6 h was 40·30 s, and at 12 h 40·80 s, compared with a pretreatment value of 130 s. During the tumour experiment there were no adverse reactions to either the first or second injection, but the repeated ether anaesthesia required led to the death of four animals.

The effect of the different treatments on pulmonary tumour formation is illustrated in *Figure 3*. Warfarin treatment again inhibited seedlings when given alone (Group 2). Median seedlings were 2 per animal in this group, compared with 16 for Group 1 animals, which received neither warfarin nor reconstitution treatment ($P<0{\cdot}05$). When tumour cells were given together with the reconstitution preparation, the results depended crucially upon the timing of the reconstitution. Where this was begun immediately (Group 3), the metastatic rate was elevated to levels even higher than for untreated control animals (median 191 *versus* 16, $P<0{\cdot}001$). When reconstitution was delayed for 12 h, by contrast, there was no discernible change in the metastatic rate (median 0 tumours *versus* 2), compared with warfarin-treated animals which did not receive any reconstitution material.

Discussion

The aim of this study was to clarify the mechanism by which warfarin inhibits metastasis of malignant tumours. In so doing, we hoped to achieve a better understanding of the metastatic process and the role of the coagulation system therein. Such an understanding may allow a more rational approach to the treatment and prevention of metastasis in human disease.

This is the first report of the use of the Mtln3/F344 tumour/host system in studies of this kind. We believe that it provides a particularly appropriate model because of its similarities to the situation in human breast cancer. The tumour is a spontaneously metastatic hormone-responsive adenocarcinoma of low immunogenicity, with histological features similar to those of the human disease[21,24]. These characteristics are uncommon in the tumour–host combinations used in previous work on the modulation of metastasis[3–6,25], and may be important in obtaining meaningful results. The use of intravenous injection for the production of model metastases has been criticized as representing only the distal part of the

Table 1 *Reconstitution experiment: Thrombotest results*

Conditions	Mean time (s)	s.e.m.	*n*
Normal F344 rats	30·60	0·73	13
Warfarin treatment	129·80	12·62	18
After 6 h reconstitution	40·30	5·37	13
After 12 h reconstitution	40·80	2·39	13

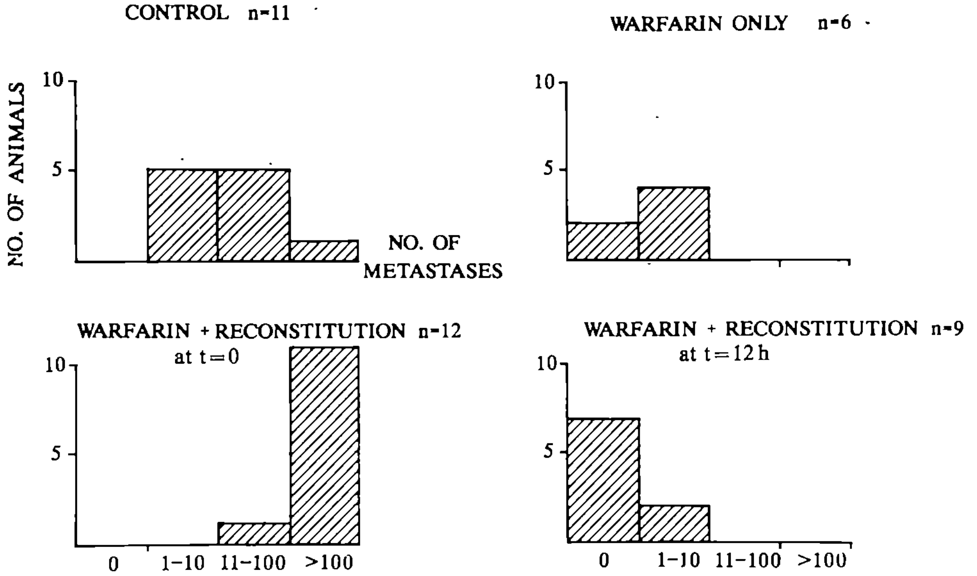

Figure 3 *Pulmonary metastases after warfarin treatment ± reconstitution of coagulation. Control* versus *warfarin only,* $P<0.05$; *warfarin + reconstitution at time 0* versus *warfarin only,* $P<0.001$; *warfarin + reconstitution at time 0* versus *control,* $P<0.001$; *warfarin + reconstitution at 12 h* versus *warfarin only,* $P>0.15$

metastatic sequence[6]. The present work, however, required manipulations that would not have been possible using a more complete model. Neither separate warfarin treatment of tumour cells and host nor restoration of normal coagulation in a warfarinized animal would have been possible in a model involving spontaneous metastasis from an implanted primary tumour. To demonstrate the relevance of our findings to true metastasis we performed an experiment using subcutaneously injected tumour cells. This showed that warfarin was equally capable of preventing metastasis in this type of model, and the inference that this occurs by the same mechanism seems probable. The method used to estimate the extent of lung metastasis is one that has been well validated in previous work[5,17,23,25]. It provides an accurate semiquantitative measure of the total number of metastases present, allowing discrimination between broad categories of light, heavy and very heavy seeding.

The effects on lung metastasis of warfarin pretreatment of the host animal and of the tumour cells were strikingly different. There was no detectable effect of pretreatment of the cells, but pretreatment of the host inhibited metastasis by about 90 per cent (*Figure 2*). Warfarin pretreatment of the cells was at a concentration higher than might be expected *in vivo*, and was sufficiently prolonged to allow effects dependent on DNA and protein synthesis to occur. If warfarin given to the animal acts directly on the tumour cells *in vivo* to inhibit metastasis, this *in vitro* pretreatment should have had at least some effect. It therefore seems that the inhibitory effect of warfarin on metastasis is mediated by some initial effect on the metabolism of the host animal.

The best known effect of warfarin in mammals is interference with the hepatic synthesis of vitamin-K-dependent coagulation factors VII, IX, X and II (prothrombin). Other vitamin K-dependent processes have been described[26], and interference with some aspect of host metabolism other than coagulation may, therefore, be responsible for the observed inhibition of tumour metastasis[5,15]. This possibility was examined in our last experiment. Here the coagulation system of the animal was effectively restored to near normal by injection of exogenous coagulation factors. Any important effects of warfarin on host metabolism, apart from those on coagulation, should therefore remain effective, but any effects on metastasis mediated via anticoagulation should be abolished. In fact, injection of coagulation factors at the time of tumour cell injection was highly successful in reversing the effects of warfarin on metastasis, and produced an excess of metastasis in treated animals over untreated controls. If the injection was delayed by only 12 h, however, this effect entirely disappeared, and there was no reversal of the warfarin-mediated suppression of metastasis (*Figure 3*).

These intriguing results suggest two interesting conclusions. First, the effectiveness of immediate reconstitution provides strong evidence for the concept that warfarin has its antimetastatic action by virtue of its anticoagulant properties. A non-coagulation-related enhancement of metastasis produced by the reconstituting material seems unlikely. This material contains negligible amounts of activated factors and no embolic aggregates, and was filter-sterilized before injection. Foreign plasma proteins *per se* are unlikely to have any marked effect on metastasis, as shown by the lack of effect of the fetal calf serum included in the cell suspension medium. The overcorrection by the reconstitution material of the warfarin effect on metastasis is not surprising, as precise control of coagulation activity was not achieved. It was not feasible in this experiment to measure Thrombotest at frequent intervals after injection of the material, and its variation over the whole period concerned is therefore unknown. It seems likely, but remains unproved, that coagulation was overcorrected during some part of the 6 h between factor injection and testing. The conflict between our findings and those of Hilgard and Maat[5] may be due to pharmacokinetic factors or to the differences in the material injected. Hilgard used a preparation of factors rich in Factor IX but containing little or no Factor VII. This was effective in restoring coagulation, but the effect was of shorter duration than in the present work. The exact importance of timing and of the influence of individual factors remains to be clarified.

Secondly, the clear difference between immediate and delayed reconstitution suggests that the major role of coagulation in the metastatic process occurs during the first 12 h after tumour cells enter the bloodstream. By the time of the delayed injection, surviving tumour cells, according to numerous previous studies[27-31], should be adherent to, and perhaps penetrating, the vascular endothelium. The time restriction found, therefore, suggests that reconstitution of coagulation affects a purely intravascular process. Ancillary effects of warfarin on tumour cells or on non-coagulation-related host protein synthesis have not been excluded, but are not likely to be important. We believe that previous reports of fibrin clots associated with the adhesion of tumour cells to the vascular endothelium[28,30] should be re-evaluated in the light of this evidence, and the role of fibrin in mediating cellular attachment to endothelial membranes defined.

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Length of stay for common surgical procedures: variation among districts

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Lengths of stay for appendicectomy, inguinal hernia repair and cholecystectomy for the 16 districts in the Northern Regional Health Authority (NRHA) and 15 districts in the South East Thames Regional Health Authority (SETRHA) are examined using data recorded in the Hospital Activity Analysis. Considerable variations exist among districts, with the three longest stay districts for each procedure in NRHA having an age-adjusted length of stay of 113 per cent of the regional average for appendicectomy, 125 per cent for hernia and 115 per cent for cholecystectomy. This resulted in >2000 additional bed days per year being occupied in the three longest stay districts in the NRHA compared with the regional average. The age adjusted length of stay for the three shortest stay districts for each procedure is 83 per cent of the regional average for appendicectomy, 75 per cent for hernia and 85 per cent for cholecystectomy. Similar differences are seen in the SETRHA, and derive from differences in the length of both pre-operative and postoperative stay. Explanations for the observed variations are considered in terms of population, organizational and clinical variables.

Keywords: Lengths of stay, discharge, Hospital Activity Analysis

A general trend in the National Health Service, as in other health systems, is the reduction in average length of hospital stay. In England and Wales in 1974 the length of stay for general surgery averaged 8·9 days, but had fallen to 7·1 days by 1984[1,2]. This reduction has been fairly uniform across age groups, specialties and operative procedures. For example, between 1974 and 1984 the mean length of stay in England and Wales for inguinal hernia repair declined from 7·3 to 4·9 days, for appendicectomy from 7·7 to 5·5 days and for cholecystectomy from 14·9 to 11·9 days.

Length of stay is one of the main clinical performance indicators, or measures of efficiency. However, while national average lengths of stay provide information on broad trends, they convey nothing about the distribution in terms of the proportion of short and long stays, or the differences between districts. Recognition of the importance of information at a local level has led the Department of Health and Social Security to develop a package of performance indicators (PIs) for English hospitals[3]. In the acute sector it provides information by district and specialty on, for example, lengths of stay and turnover, costs per case, and in-patient spending per district resident, for all acute patients. However, of greater relevance to clinicians is the variation in performance for specific diagnoses and operative procedures.

This study examines the variation in lengths of stay for three common surgical procedures among District Health Authorities in the South East Thames Regional Health Authority (SETRHA) and the Northern Regional Health Authority (NRHA). The effects of pre- and postoperative stay, and of long and shorter stay cases in contributing to the observed variations are examined and an assessment made of their implications for resource use and patient throughput. Possible explanations in terms of population, organizational and clinical factors are considered.

Data and methods

Statistics on hospital use are collected in the Hospital Activity Analysis (HAA) produced by each Regional Health Authority. National summary statistics are derived from a 10 per cent sample of these regional data. This study employs 1982 HAA data for the 15 Health Districts in the SETRHA and 1984 HAA data for the 16 Health Districts in the NRHA, which was the most recent data available. In each case the district employed is that of treatment.

The analysis is based on three operative conditions: inguinal hernia repair (410–411), appendicectomy (440–445) and cholecystectomy (522). Appendicectomy is the most common non-elective general surgical procedure and inguinal hernia repair the most common elective procedure. Cholecystectomy, another common surgical procedure, is characterized by an older age distribution and therefore longer mean length of stay.

Patients recorded as undergoing a second procedure are excluded from the analysis with the exceptions of appendicectomy with laparotomy, and cholecystectomy with cholangiography, to produce a more homogeneous series of cases. As a result of these exclusions the sample cases in SETRHA and NRHA accounted for 95 and 84 per cent of in-patient admissions for appendicectomy respectively, 74 and 87 per cent of admissions for inguinal hernia repair, and 76 and 74 per cent of cholecystectomies. The large proportion of cholecystectomies excluded reflects the tendency for other procedures to be undertaken at the same time, such as operations on the common bile duct, appendicectomy and gastric intubation. Also excluded are cases of day surgery for inguinal hernia repair. Recorded cases of day surgery were mainly concentrated in the group aged under 25 where they formed 17 and 14 per cent of inguinal hernias in the SETRHA and NRHA respectively, compared with <0·3 per cent of inguinal hernia repairs for those aged 25 and over.

Lengths of stay >28 days were aggregated in the data provided by the NRHA. These cases form only 0·5 per cent of hernia admissions, 0·4 per cent of appendicectomies and 2·1 per cent of cholecystectomies in NRHA, with the percentages being almost identical in SETRHA. In the analysis the median value of all lengths of stay >28 days in SETRHA (50 days for hernia, 35 days for appendicectomy and 36 days for cholecystectomy) is assigned to lengths of stay of >28 days in each region.

The age distribution of patients for each procedure is similar for the two regions, but varies between districts. A score standardized for age is therefore used to compare lengths of stay between districts for each operation. The age groups employed are those in which the procedure is most common to reduce the possible distortions introduced by small numbers of cases (see note to *Table 1*). For inguinal hernia the youngest age group is also excluded to remove the case mix problem of including

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Table 1 *Distribution of cases by age and operative procedure in two regional health authorities*

Age group (years)	NRHA, 1984 Appen-dicectomy (%)	NRHA, 1984 Inguinal hernia (%)	NRHA, 1984 Chole-cystectomy (%)	SETRHA, 1982 Appen-dicectomy (%)	SETRHA, 1982 Inguinal hernia (%)	SETRHA, 1982 Chole-cystectomy (%)
0–24	66	19	3	67	18	4
25–44	21	15	26	21	14	26
45–64	9	37	44	8	35	41
65–74	3	19	19	2	21	19
>74	1	10	8	1	13	10
Total	100	100	100	100	100	100
(*n*)	(3694)	(3705)	(2287)	(4407)	(4687)	(1879)

The age groups employed in ranking districts were: appendicectomy (0–24, 25–44, 45–64), inguinal hernia (25–44, 45–64, 65–74) and cholecystectomy (25–44, 45–64 and 65–74)

Table 2 *Mean and median lengths of stay and 95 per cent range by age and operative procedure in two health authorities*

Age group (years)	NRHA, 1984 Appen-dicectomy (%)	NRHA, 1984 Inguinal hernia (%)	NRHA, 1984 Chole-cystectomy (%)	SETRHA, 1982 Appen-dicectomy (%)	SETRHA, 1982 Inguinal hernia (%)	SETRHA, 1982 Chole-cystectomy (%)
<25	4·9	2·7	8·5	5·0	3·0	9·3
	5	2	8	5	2	8·7
	(2–10)	(1–7)	(4–16)	(2–10)	(1–8)	(4–17)
25–44	5·5	4·4	9·2	5·5	4·8	9·6
	5	4	9	5	4	9
	(2–12)	(1–10)	(4–17)	(2–12)	(2–11)	(4–18)
45–64	7·5	4·7	10·5	7·2	5·5	10·7
	7	4	10	6	5	10
	(3–17)	(2–11)	(4–21)	(2–18)	(2–12)	(45–21)
65–74	10·0	6·0	12·9	10·0	6·0	12·7
	9	5	11	9	5	11
	(3–27)	(2–15)	(5–29)	(3–25)	(2–14)	(5–28)
>74	15·3	8·2	16·5	11·6	7·9	14·5
	13	7	15	10	7	13
	(4–40)	(2–22)	(6–38)	(3–32)	(2–21)	(5–36)
All ages						
Mean	5·5	4·9	11·0	5·5	5·4	11·1
Median	5	4	10	5	5	10
95% range	(2–12)	(1–14)	(4–23)	(2–12)	(1–15)	(4–23)

young children with adults. Since length of stay distributions are strongly positively skewed, the log length of stay is used to normalize the data. For each patient a score $S=(L-M_{AOR})/SD_{AOR}$ is calculated, where: L is the log length of stay for that patient; M_{AOR} is the mean log length of stay for patient in age group A undergoing operation O in region R; and SD_{AOR} is the standard deviation (log length of stay) for patient in age group A undergoing operation O in region R. Thus S is an age adjusted score representing the distance of the patient from the regional mean for his age group for that operative procedure, expressed in units of standard deviation. Analysis of variance shows statistically significant differences between districts in their mean age adjusted score for each operation. Districts are therefore ranked for each operation according to their mean age adjusted score. Comparisons are then made between the regional average length of stay in each age group and the corresponding length of stay in the three highest and three lowest ranking districts for each procedure.

Results

Length of stay

Each operative procedure shows an increasing length of stay with rising age (*Table 2*). The main difference between the regions is the steeper increase in lengths of stay among the age group 75 years and over in NRHA, although the numbers in this age group are small. However, despite the general association between age and increasing length of stay, a considerable spread of lengths of stay within age groups for each operative procedure is indicated by the 95 per cent range.

Table 3 ranks the districts within each region by length of stay based on their standardized score. Some districts feature fairly consistently at the high or low end of the distribution for each procedure, others rank very differently according to procedure. Only three districts ranked as long or short stay for each of the three procedures.

The length of stay profiles for the three shortest stay districts for each procedure are very similar in the two regions, as are the length of stay profiles for the three longest stay districts (*Table 4*). Within each region the greater overall mean stay in the longest stay districts is due to a shift in the whole length of stay distribution, i.e. to large numbers of patients staying one or two additional days rather than to a small number of long stay cases. An analysis of admissions staying 29 days and over showed that in the three longest stay districts in NRHA they formed 0·8 per cent admissions for hernia repair, 0·7 per cent admissions for appendicectomy and 3·5 per cent admissions for cholecystectomy, compared with figures for the three shortest stay districts of 0·7, 0·4 and 1·4 per cent respectively. The differences are very similar for SETRHA.

The length of stay for all age groups in NRHA range from

Table 3 *Ranking of districts by length of stay for selected procedures using a standardized score*

District	NRHA, 1984 Appendicectomy	NRHA, 1984 Inguinal hernia	NRHA, 1984 Cholecystectomy	SETRHA, 1982 Appendicectomy	SETRHA, 1982 Inguinal hernia	SETRHA, 1982 Cholecystectomy
A	1	2	1	1	1	8
B	2	5	4	2	5	6
C	3	7	3	3	4	1
D	4	4	11	4	7	7
E	5	1	5	5	14	5
F	6	15	12	6	12	12
G	7	11	8	7	2	3
H	8	8	2	8	15	4
I	9	6	15	9	8	13
J	10	10	13	10	3	2
K	11	12	6	11	10	10
L	12	9	7	12	11	15
M	13	14	10	13	13	14
N	14	13	9	14	6	9
O	15	3	14	15	9	11
P	16	16	16			
Minimum no. of patients per district	105	110	44	163	139	57
Maximum no. of patients per district	532	666	382	490	552	188

For the ranking, 1 = shortest stay

83 per cent of the regional average for appendicectomy in the three shortest stay districts to 113 per cent in the three longest stay districts. The corresponding range for hernia repair is 75 to 125 per cent and for cholecystectomy 85 to 115 per cent. The range for appendicectomy and cholecystectomy in SETRHA is very similar to NRHA although slightly reduced for hernia (*Table 5*). The observed differences in overall lengths of stay for hernia and cholecystectomy are due in part to the duration of pre-operative stay. In the three shortest stay districts in SETRHA, 97 per cent of hernia admissions and 84 per cent of cholecystectomy admissions have a pre-operative stay of less than two days, whereas the corresponding percentages are 81 and 50 per cent for the three longest stay districts (*Table 6*).

Bed days occupied

The three longest stay districts occupy > 2000 bed days per year above the regional average for the three selected procedures (*Table 7*). Assuming the overall mean stay for all ages in the region (*Table 2*) and an 80 per cent occupancy, these 'additional' bed days in the three longst stay districts in NRHA would allow an increase in throughput of 10 per cent for appendicectomy, 21 per cent for hernia and 12 per cent for cholecystectomy. The corresponding figures for SETRHA are 11, 13 and 12 per cent respectively.

Case mix

The proportion of cases excluded due to a second procedure are almost identical in the longest and shortest stay districts for each operative condition, although exclusions were more common among patients aged 65 and over than for younger age groups. Two sub-groups expected to be associated with higher complication rates and greater lengths of stay are drainage of appendix abscess and strangulated hernias. However only 15 cases of drainage of appendix abscess (0·4 per cent of admissions) and 14 cases of strangulated hernia (0·4 per cent of admissions) are recorded in NRHA, and 22 cases of appendix abscess (0·6 per cent of admissions) and 40 admissions for strangulated hernia (0·9 per cent) in SETRHA. Data was available on the distribution of strangulated hernia in SETRHA and shows they are slightly more common in the shortest stay districts (2 per cent admissions) than in the longest stay districts (0·9 per cent admissions). They cannot therefore account for the observed differences in length of stay profiles.

Type of discharge

In SETRHA 97 per cent of admissions for these three procedures are discharged directly to home, 2·7 per cent to other hospitals or convalescent units and 0·3 per cent died. The proportions are similar for NRHA, with 98 per cent of admissions discharged to home, 1·9 per cent to other hospitals or convalescent units and 0·3 per cent died. However, although < 3 per cent of admissions in each region are discharged to other hospitals or units, a couple of districts deviated significantly from this pattern. In SETRHA district C, 19 per cent of hernia admissions, 20 per cent of appendicectomy admissions and 31 per cent of cholecystectomy admissions are discharged to another hospital or convalescent unit, with a correspondingly smaller proportion being discharged directly to home. The high transfer rate in this district held for all ages but is most common among elderly patients. In NRHA region a high transfer rate occurred in district L, with 6 per cent of appendicectomy admissions, 8 per cent of hernia admissions and 27 per cent of cholecystectomy admissions being discharged to another hospital or convalescent unit.

Discussion

Substantial differences exist between districts in lengths of in-patient stay for common surgical procedures. For both regions the greater mean stay in 'long stay' districts is accounted for by a shift in the entire distribution of lengths of stay, with most patients spending a few extra days in hospital, rather than being explained solely by a greater prevalence of long stay cases. For hernia repair and cholecystectomy this was associated with a longer pre-operative and postoperative stay, although the latter makes a greater contribution to the overall differences. An indication of the resource implications of the variations in lengths of stay is gained by taking the regional average as a standard for comparison, albeit recognizing that this does not necessarily represent good practice. Over 2000 fewer bed days per year would have been occupied in both NRHA and SETRHA for the three selected procedures if their three longest

Table 4 *Length of stay distributions for the three districts in SETRHA 1982 ranked as having the lowest and highest stays for each procedure**

	<45 years		45–64 years	
Length of stay for appendicectomy (days)	Shortest stay districts (%)	Longest stay districts (%)	Shortest stay districts (%)	Longest stay districts (%)
1–2	11	1	11	—
3–4	51	31	19	14
5–6	27	38	38	29
7–8	8	20	12	18
>8	4	9	20	39
Total	100	100	100	100
(*n*)	(673)	(699)	(90)	(90)

	<45 years		45–64 years		>64 years	
Length of stay for inguinal hernia (days)	Shortest stay districts (%)	Longest stay districts (%)	Shortest stay districts (%)	Longest stay districts (%)	Shortest stay districts (%)	Longest stay districts (%)
1–2	49	31	15	1	10	5
3–4	37	28	53	25	38	17
5–6	9	18	23	26	27	31
7–8	2	16	7	27	13	23
>8	3	7	2	20	12	24
Total	100	100	100	100	100	100
(*n*)	(284)	(332)	(367)	(330)	(392)	(259)

	<45 years		45–64 years		>64 years	
Length of stay for cholecystectomy (days)	Shortest stay districts (%)	Longest stay districts (%)	Shortest stay districts (%)	Longest stay districts (%)	Shortest stay districts (%)	Longest stay districts (%)
1–4	5	—	3	1	4	—
5–6	35	9	18	—	15	1
7–8	37	22	34	12	18	10
9–10	10	32	22	23	19	16
11–12	8	14	8	27	13	23
13–14	—	8	5	16	8	19
15 and over	6	14	11	21	22	30
Total	100	100	100	100	100	100
(*n*)	(98)	(117)	(153)	(164)	(120)	(79)

* See *Table 3*

Table 5 *Observed length of stay for short and long stay districts in SETRHA 1982 as a percentage of the regional average*

	Three shortest stay districts			Three longest stay districts		
Age group (years)	Appendicectomy (%)	Inguinal hernia (%)	Cholecystectomy (%)	Appendicectomy (%)	Inguinal hernia (%)	Cholecystectomy (%)
0–24	91	82	95	115	109	111
25–44	81	74	81	115	127	115
45–64	77	77	88	104	121	116
65–74	78	82	85	122	115	121
>74	93	94	86	112	103	93
All ages SETRHA	87	82	86	114	116	115
All ages NRHA	83	75	85	113	125	115

stay districts had experienced the same length of stay as the regional average, thus pointing to the possible scope for a significant increase in turnover. The bed days saved would of course be considerably greater if the longest stay districts were to move closer to the pattern for the three shortest stay districts, which occupy ≈2000 fewer bed days than the regional average.

The observed variations in lengths of stay raises questions of the accuracy of HAA data. However, although errors of recording and coding are known to occur, these are likely to be much less for common surgical procedures compared with more complex conditions and diagnoses[4]. In addition, only a large and consistent bias could produce the observed variations. It is

Table 6 *Distribution of pre-operative length of stay for short and long stay districts in SETRHA 1982*

	Appendicectomy		Hernia		Cholecystectomy	
Pre-operative stay (days)	Three shortest stay districts (%)	Three longest stay districts (%)	Three shortest stay districts (%)	Three longest stay districts (%)	Three shortest stay districts (%)	Three longest stay districts (%)
0	78	73	25	20	5	6
1	19	23	72	61	79	44
2	2	2	1	11	4	20
3	2	2	1	3	2	12
>3			1	5	10	18
Total	100	100	100	100	100	100
(*n*)	(763)	(789)	(1043)	(921)	(371)	(360)

Table 7 *Bed days occupied in short and long stay districts compared with an expected rate based on the regional average*

	Three shortest stay districts			Three longest stay districts		
Bed occupied (days)	Appendicectomy	Hernia	Cholecystectomy	Appendicectomy	Hernia	Cholecystectomy
NRHA 1984						
Actual use	2536	2426	3929	5414	4057	5872
Difference between actual and expected use	−522	−792	−665	+602	+822	+761
SETRHA 1982						
Actual use	3629	4706	3587	4959	5594	4489
Difference between actual and expected use	−552	−1042	−582	+618	+785	+577

thus necessary to examine the possible causes of the relatively long lengths of stay in some districts in terms of population, organizational and clinical variables.

The need for hospital services is affected by the socio-economic composition of the population, and especially the presence of deprivation. Recognizing this the Resource Allocation Working Party incorporated mortality rates in the form of standardized mortality ratios (SMRs) as a proxy measure of morbidity into the formula used in allocating resources for acute hospitals[5]. The adequacy of SMRs, especially at the sub-regional level, has been criticized for not encompassing the wider needs for hospital care which arise as a direct result of poor social conditions (e.g. poor housing or elderly persons living alone)[6]. However, studies based on the analysis of individual cases indicate that the influence of unfavourable social circumstances in prolonging length of stay generally depends on patients' associated medical condition and level of dependency, and mainly affects elderly patients[7,8]. Differences in the social characteirstics of patients is thus unlikely to account for the greater lengths of stay among all age groups in the longest stay districts.

A major determinant of variations in hospital use is the supply of beds, with thresholds for referral, admission and discharge when considered at an aggregate level being related to current levels of provision or those which obtain in the recent past[9–11]. In addition to these variations in acute hospital provision are differences in the provision of convalescent and nursing facilities to cater for patients with low levels of medical and nursing needs. The rate of transfer to other facilities thus needs to be taken into account in interpreting HAA data on lengths of stay and in considering the total resources used by each district for particular patient groups.

The organization and deployment of resources at the hospital level may also contribute to the observed variations by affecting the time required for different activities, such as routine tests, medical procedures and arrangements for discharge. The scope for increasing administrative efficiency may however be limited by the availability of staff, theatres, etc. and by the requirements of teaching. A further constraint on reducing lengths of stay can be the financial implications, because if this results in a greater throughput then total costs are increased although the cost per case is reduced.

The determinants of length of stay under most immediate clinical control include decisions as to the timing of surgery, the requirements for pre-operative investigation, the specific surgical techniques employed and general length of stay norms. There is little information on the variation in or precise impact of these variables at a local level. Changes in techniques are however a major factor responsible for the general decline in length of stay for many surgical procedures[12]. Evaluations of inguinal hernia repair have similarly drawn attention to the effects of different techniques and types of anaesthesia on lengths of postoperative stay and recurrence rate[13–15].

HAA data, although valuable in monitoring length of stay, do not allow conclusions to be drawn as to the underlying causes of the observed variations or the appropriateness of current practices. However, a comparative profile of deviations from the regional average for frequently performed procedures does provide a useful yardstick for assessing performance, which avoids the case mix problem of specialty data. The identification of significant variations should encourage reviews of current practices. This might involve an extension of the audits already undertaken by some surgical firms[16,17], to include the comparison of organizational and clinical practices in districts identified as having relatively long or short stays. This could be complemented by reviews of the medical and social needs of patients occupying beds in the longest stay districts, and by studies of the effects of different lengths of stay on demands for community services and patients' well-being following discharge.

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Pre-operative assessment of fitness score

Death within 30 days or survival after a major operation depends on three things: the severity of the disease and the operation, the technical proficiency of the surgeon and the ability of the patient to withstand both disease and operation. The first of these can be estimated by reference to published figures, the second can only be guessed at and the third has in the past been a matter of subjective judgement. With the aim of producing an objective assessment of the likelihood of survival, we have constructed a score system comprising 26 items including age, chronic disease and acute presenting disease. These items are each given a weight of 1 to 4 and the total fitness score for any patient ranges from 0 (fit) to 10 (unlikely to survive). We have validated this score prospectively in 1517 consecutive patients undergoing emergency or elective major abdominal operations (excluding appendicectomies and hernia repairs). In 492 operations in which the patient scored 0 or 1, one patient died (0·2 per cent); in 290 with scores of 2 or 3, one died (0·3 per cent); in 313 with scores of 4 or 5, five died (1·6 per cent). It was when the score rose to 6 or over that the chances of survival progressively declined: 16 died of the 105 patients who scored 6 (15·2 per cent) as did 74 of the 191 who scored 7 or 8 (38·7 per cent) and 70 of the 126 who scored 9 or 10 (55·6 per cent). We now use the score as part of our audit and enquire particularly closely into the death of any patient with a pre-operative score of less than 6.

Keywords: Surgery, postoperative complications, mortality, morbidity

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A Confidential Enquiry into Postoperative Deaths (CEPOD) was initiated in 1984 by the Association of Surgeons of Great Britain and Ireland and the Association of Anaesthetists of Great Britain and Ireland. The enquiry is carried out by assessors who are sent anonymous details of patients who have died after operations; the assessors are required to judge whether any aspect of the treatment was substandard. One of their difficulties is in estimating how fit the patient was for the operation performed.

As we found that existing methods of assessment of the risks of operation were both subjective and unreliable, we devised a simple scoring method which fits into our computerized audit system. We gave points not only for the extent of chronic deterioration of vital organs but also for the patient's age and the severity of the presenting disease. We used the results of only three laboratory tests because, in many emergencies, other tests are not available.

Patients and methods

We studied 1517 consecutive patients aged between 12 and 96 years who underwent major abdominal operations. We excluded those having appendicectomies and hernia repairs because the rates of major complications are negligible after these operations. Seven hundred and sixty-four patients were admitted for elective operations and 753 as emergencies, and these were operated on either immediately after resuscitation or after medical treatment and investigation. There were 820 men and 697 women; 701 patients (46·2 per cent) were over the age of 70 years, the mean age of all patients being 65·1 years. Four hundred and eighty-two operations (31·8 per cent) were for cancer, more than half of them (266) being palliative.

We allotted a pre-operative assessment of fitness score (PAFS) to each patient: this was the total of the scores for all risk factors listed in *Table 1*. The weight given to each factor was arbitrary and reflected our judgement in the first 500 patients studied.

We classified complications as major infective (sepsis and pneumonia), major non-infective (organ failure without sepsis), minor infective (including minor wound infections, purulent sputum and asymptomatic bacteriuria) and minor non-infective; each patient's progress was recorded for at least 30 days or until death.

We used the linear trend in proportions test to estimate statistical probabilities from a 2 × 10 contingency table.

Results

Two hundred and ninety-eight of the 1517 operations were followed by major complications (19·6 per cent); 167 (56·0 per cent) of these patients died (*Tables 2* and *3*). The incidence of major complications was low in the group in whom the PAFSs were less than 6: among these 1095 patients there were 102 such complications (9·3 per cent) and 7 deaths (0·6 per cent). By contrast, when the PAFSs were 6 or more there were 196 major complications after 422 operations (46·4 per cent) and 160 deaths (37·9 per cent). The proportion of major complications which ended in death was 7 out of 102 (6·9 per cent) in the low-scoring patients and 160 out of 196 (81·6 per cent) in those with a PAFS of 6 or more. The rate of major complications after emergency or urgent operations was twice the rate after elective operations and the death rate was more than three times as great (*Table 3*).

We were particularly concerned about the seven patients who died and whose PAFSs were less than 6. Details of these patients are given in *Table 4*.

The sensitivity of the PAFS in predicting death (taking a score of 0–5 as low risk and one of 6–10 as high risk) was 95·8 per cent and its specificity 80·6 per cent. The increase in proportions of deaths and major complications with increasing PAFS was significant, but no such correlation was found between PAFS and minor complications.

Discussion

The success of an operation depends on a number of factors, prominent among which are the nature of the disease for which

Table 1 *Pre-operative assessment of fitness score*

Score 1 for each:
- Cardiac symptoms controlled by treatment
- Short of breath on climbing stairs
- Morning cough
- Stroke or myocardial infarct >6 months ago
- Haemoglobin <10 g/dl
- Serum albumin 30–35 g/l
- Plasma urea 10–19 mmol/l
- Steroid treatment
- Controlled diabetes

Score 2 for each:
- Age 70–79
- Cardiac symptoms poorly controlled by treatment
- Short of breath on walking
- Persistent cough with sputum

Score 3 for each:
- Clinical jaundice
- Serum albumin <30 g/l
- Loss of 10% weight in one month
- Plasma urea >20 mmol/l
- Short of breath at rest
- Myocardial infarct within 6 months
- Confusion
- Cytotoxic treatment

Score 4 for each:
- Age >80 years
- Palliative operation for cancer
- Intestinal obstruction
- Perforations, pancreatitis and intraperitoneal abscess (not including perforated appendicitis)
- Haemorrhage or anaemia requiring transfusion

the operation is undertaken, the quality of care, and the ability of the patient to withstand the insults of both the disease and the operation. The American Society of Anesthesiologists' division into five classes of fitness for operation[1] suffers from the disadvantage of making no allowance for the severity of either the presenting disease or the proposed operation, and the index of cardiac risk in general surgical patients[2] has regard for cardiac causes of death alone. It is the assessment of patients' ability to survive potentially lethal diseases and operations that has attracted so much attention in recent years—attention that has focused on nutritional status almost to the exclusion of other indicators of risk.

Starvation reduces the body reserves of protein, but the suggestion that it is a principal cause of postoperative complications is too simplistic. Gottlieb[3] reported his experiences as a medical officer in a Japanese prisoner-of-war camp in the Second World War:

> Excellent results were obtained in abdominal surgery, even though there was very little asepsis, for our home-made steriliser was inadequate and our gloves were merely dipped in creosote solution, plus the fact that both the air and the operating room were constantly being contaminated by dust and dirt. We applied sulfanilamide intraperitoneally, and along the tissue planes in all cases, using about 10 g for each case. There was no postoperative peritonitis, very little abdominal distension and no stitch abscesses appeared... an interesting observation is that men who in ordinary times would be considered very poor surgical risks because of their emaciation, their amoebiasis, and their vitamin deficiencies responded very well under surgery.

There are many ways of measuring malnutrition, of which probably the most important is 'carefully performed history taking and physical examination'[4]. Low serum concentrations of albumin, pre-albumin and transferrin[5,6] are associated with an increased incidence of postoperative complications; these, however, usually reflect pre-existing disease rather than malnutrition. The third group of measurements which have been studied are the anthropometric indices: triceps skinfold thickness and midarm circumference. To these must be added the tests of muscle function: handgrip dynamometry[7], and contraction force and relaxation time of adductor pollicis muscle produced by electrical stimulation[8,9]. The influence of cell-mediated immunity has been stressed by Meakins and his colleagues[10] who found that pre-operative anergy to five recall antigens predicted a high rate of postoperative septic complications and death; other workers, however, were unable to confirm these findings[11,12].

This concentration on measurements of malnutrition has to some extent obscured the fact that many patients die or suffer major complications after operations, not because they lack the ability to divert nutrients to the fight against injury and infection, but because of the uncorrectable progress of their presenting disease and the wearing out of vital organs. It was in an attempt to incorporate some assessment of these risk factors that we devised the PAFS. We have shown that the score broadly predicts the incidence of major complications and death. We are left with the few patients with low pre-operative scores who died, and the larger number of those with high scores who survived without complications. It is clear, on the one hand, that the death of any patient with a pre-operative score of less than 6 requires special attention and, on the other, that we have not produced a specific enough system—17 per cent of the patients who scored 9 or 10 survived without complications.

Table 2 *PAFS and postoperative complications: elective admissions*

		Complications			
Score	Deaths (%)*	Major (%)†	Minor (%)‡	None (%)	Total
0	1 (0·3)	14 (4·3)	56 (17·1)	257 (78·6)	327
1	0	6 (9·8)	22 (36·1)	33 (54·1)	61
2	1 (0·8)	12 (9·9)	28 (23·1)	81 (66·9)	121
3	0	6 (9·1)	13 (19·7)	47 (71·2)	66
4	2 (3·1)	12 (18·8)	14 (21·9)	38 (59·4)	64
5	0	5 (16·1)	14 (45·2)	12 (38·7)	31
6	4 (16·7)	7 (29·2)	10 (41·7)	7 (29·2)	24
7	14 (51·9)	17 (63·0)	4 (14·8)	6 (22·2)	27
8	8 (34·8)	10 (43·5)	4 (17·4)	9 (39·1)	23
9	5 (41·6)	6 (50·0)	3 (25·0)	3 (25·0)	12
10	3 (37·5)	4 (50·0)	1 (12·5)	3 (37·5)	8
Total	38 (5·0)	99 (13·0)	169 (22·1)	496 (64·9)	764

* $\chi^2 = 155{\cdot}3$, d.f. $= 1$, $P < 0{\cdot}001$, *versus* none
† $\chi^2 = 108{\cdot}9$, d.f. $= 1$, $P < 0{\cdot}001$, *versus* none
‡ $\chi^2 = 2{\cdot}1$, d.f. $= 1$, $P = 0{\cdot}15$, *versus* none

Table 3 *PAFS and postoperative complications: emergency admissions*

		Complications			
Score	Deaths (%)*	Major (%)†	Minor (%)‡	None (%)	Total
0	0	2 (2·2)	16 (18·0)	71 (79·8)	89
1	0	3 (20·0)	2 (13·3)	10 (66·7)	15
2	0	6 (10·0)	20 (33·3)	34 (56·7)	60
3	0	5 (11·6)	20 (46·5)	18 (41·9)	43
4	2 (1·3)	22 (13·8)	48 (30·2)	89 (56·0)	159
5	1 (1·7)	9 (15·3)	27 (45·8)	23 (39·0)	59
6	12 (14·8)	18 (22·2)	23 (28·4)	40 (49·4)	81
7	29 (41·4)	37 (52·9)	18 (25·7)	15 (21·4)	70
8	23 (32·4)	25 (35·2)	22 (31·0)	24 (33·8)	71
9	46 (65·7)	47 (67·1)	14 (20·0)	9 (12·9)	70
10	16 (44·4)	25 (69·4)	5 (13·9)	6 (16·7)	36
Total	129 (17·1)	199 (26·4)	215 (28·6)	339 (45·0)	753

* $\chi^2 = 183{\cdot}8$, d.f. $= 1$, $P < 0{\cdot}001$, *versus* none
† $\chi^2 = 141{\cdot}1$, d.f. $= 1$, $P < 0{\cdot}001$, *versus* none
‡ $\chi^2 = 0{\cdot}3$, d.f. $= 1$, $P = 0{\cdot}58$, *versus* none

Table 4 *Details of seven patients with low PAFS who died*

Sex	Age	Score	Disease and operation	Urgency	Complications	Day of death	Autopsy?	Cause of death	Comment
M	61	0	A–P excision for rectal carcinoma	Elective	None	6	Yes	Pulmonary embolism	Routine low-dose subcutaneous heparin
F	54	5	Laparatomy/biopsy: retroperitoneal lymphosarcoma	Elective	Severe pancytopenia, melaena	18	Yes	Lymphomatous replacement of bone marrow	
M	70	4	A–P excision for rectal carcinoma	Elective	Burst abdomen	10	Yes	Myocardial infarct	
M	61	2	Superior mesenteric artery occlusion: bypass graft	Elective	Intestinal gangrene	7	Yes	Intestinal gangrene	Failure of bypass graft
M	77	4	Colostomy closure: sigmoid carcinoma	Elective	None	7	Yes	Pulmonary embolism	No DVT prophylaxis
F	64	4	Resection for sigmoid carcinoma	Elective	Sepsis	4	No	Probable anastomotic dehiscence	Permission for autopsy refused
M	63	4	Ruptured aortic aneurysm: laparotomy	Emergency	Shock	0	Yes	Haemorrhagic shock	Died on opening abdomen

DVT, deep vein thrombosis

We conclude that the score system that we have devised, although it has many deficiencies, fairly accurately reflects the prognosis after major abdominal operations.

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Selection of patients for surgery following peptic ulcer haemorrhage

Surgery remains the only widely available and well-proven means of stopping haemorrhage from peptic ulcers and preventing its recurrence but carries an unavoidable morbidity. If surgery is to be used to maximum effect with minimum morbidity, an accurate means of predicting which patients will suffer further haemorrhage is needed. Although over 80 per cent of patients who rebleed have the endoscopic stigmata of haemorrhage, a policy of operation in all patients with stigmata would lead to a very high operation rate and a high proportion of unnecessary operations, as one-half of the patients with stigmata do not rebleed. Clinical data were collected prospectively from 278 cases of peptic ulcer haemorrhage. The data from a randomly selected 75 per cent of the cases were analysed by stepwise logistical regression. Patients who had the endoscopic stigmata of haemorrhage and who had a probability of further haemorrhage, calculated from the regression equation, of more than 0·2 were identified as a high risk group. This definition was validated using the 25 per cent of cases not used in the initial analysis. Eighty-four per cent of patients in the high risk group suffered further haemorrhage and all such patients therefore require early surgery: such a policy would have resulted in an operation rate of 28 per cent. Thirty per cent of the patients who had further haemorrhage were not identified as being at high risk but none of them had a severe rebleed. The regression equation greatly enhanced the value of stigmata in guiding surgical decision making and merits further evaluation.

Keywords: Peptic ulcer haemorrhage, endoscopy, stigmata of haemorrhage

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The place of surgery in the management of peptic ulcer haemorrhage remains controversial[1–3]. Despite advances in pharmacology and therapeutic endoscopy, surgery remains the only widely available and well-tried means of stopping haemorrhage or preventing its recurrence. Equally, surgery carries an unavoidable morbidity and mortality, especially in the age group most commonly affected by peptic ulcer haemorrhage.

This controversy was partly resolved by a clinical trial carried out at the Birmingham General Hospital[3]. Patients were randomized to be managed under an aggressive or a conservative surgical policy. In patients under 60 years of age there were no deaths, justifying the conservative policy in this age group; in patients aged 60 years or more, however, the aggressive policy was associated with significantly fewer deaths.

The operation rate in aggressively treated patients in this trial was 59 per cent but the rebleeding rate in conservatively treated patients was only 27 per cent, suggesting that over one-half of those who had operations in the first group would not have rebled and that their operations were unnecessary. This is an inescapable consequence of the inaccuracy of existing methods of predicting which patients will, in fact, rebleed. The best indicator of the likelihood of rebleeding is the presence of the endoscopic stigmata of recent haemorrhage but only 24–51 per cent of patients with stigmata do rebleed[4–6] and only 12 per cent die[6].

For surgery to be used to maximum effect with minimum morbidity, a more accurate means of predicting which patients will rebleed is required. Between 1979 and 1984 a prospective study of all patients admitted to the Birmingham General Hospital with upper gastrointestinal haemorrhage was carried out. The data from patients with bleeding peptic ulcers were analysed by stepwise logistical regression in order to develop a method of predicting further haemorrhage which might serve as a guide to surgical intervention.

Patients and methods

All patients admited to the Birmingham General Hospital with upper gastrointestinal bleeding between September 1979 and December 1984 were studied prospectively. From October 1980, patients who developed bleeding following admission for another cause were also included. Patients were considered to have bled if they or a witness gave a convincing history of the vomiting of red blood or if there was tarry black stool in the rectum. Patients who had vomited black granular material ('coffee grounds') were not included unless they had other convincing signs of bleeding.

Arrangements were made for emergency endoscopy to be done as soon as the patient was admitted. Endoscopies took place at any hour of the day or night, as soon as the patient was adequately resuscitated and always within 4 h of admission. After endoscopy, patients were admitted to a designated GI bleeding unit and managed jointly by the admitting medical firm and a multidisciplinary GI bleeding team, of which the authors were the principal members. Management was standardized, especially in respect of the criteria for surgical intervention.

A standard set of data were collected prospectively for each patient (*Table 1*). Particular attention was paid to the precise definition of each variable. The endoscopic stigmata of recent haemorrhage were recorded individually but, for the purpose of statistical analysis, the stigmata which have been shown to carry prognostic significance (bleeding, visible vessel, adherent clot)[6] were grouped together under the heading 'major stigmata'. Persistent or recurrent haemorrhage ('further haemorrhage') was diagnosed if the patient continued to have red haematemesis or had further melaena associated either with haemodynamic evidence of bleeding or with a fall in the haemoglobin concentration of at least 2 g/dl occurring more than 24 h after the cessation of bleeding and transfusion.

The data were stored on the Honeywell DPS8/70M mainframe computer at the University of Birmingham. The association between each of the clinical variables and the occurrence of further haemorrhage

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Table 1 *Standard set of data collected prospectively from all patients presenting with upper gastrointestinal haemorrhage*

Presenting features	
Age	Pulse
Sex	Blood pressure
Haematemesis/melaena	Haemoglobin concentration
Duration recent symptoms	Concurrent diseases
Total duration symptoms	Source of haemorrhage
Previous bleed	Endoscopic stigmata
Previous ulcer surgery	Units transfused
Smoking	Delay before surgery
Drinking	
Drug usage	
Outcome	
Further haemorrhage	Emergency surgery
Death	In-patient stay

Table 2 *Categorical variables significantly associated with further haemorrhage from peptic ulcers* (χ^2 *test*)

Variable	Relative risk	P
Age ≥ 60 years	1·7	< 0·05
Taking medication	1·7	< 0·05
Shock*	2·0	< 0·002
Haemoglobin < 10 g/dl	2·0	< 0·02
Major stigmata	6·1	< 0·0001
Gastric ulcer	1·7	< 0·008

* Shock = pulse ≥ 100 beats/min and systolic blood pressure < 100 mmHg

was tested in the group of patients bleeding from peptic ulcers. Four patients who had not been resuscitated because of serious co-existing disease were excluded from this analysis, as were all patients who had been randomly allocated to treatment under the aggressive surgical policy in the clinical trial conducted at the same hospital between 1981 and 1983[3], many of whom had had very early operations and who had not therefore had a chance to rebleed. The Statistical Package for the Social Sciences and the BMDP Statistical Software Package were used for the statistical analysis. Associations involving categorical variables were tested by the χ^2 test. The Mann–Whitney *U* test was used for continuous variables.

All variables were included in an analysis of the risk of further haemorrhage by stepwise logistical regression. This analysis was carried out using a randomly selected 75 per cent of the cases and the predictive value of the resulting regression equation was assessed using the remaining 25 per cent of the cases. The sensitivity and specificity of the predictions were calculated by the method of McNeil *et al.*[7].

Results

Six hundred and nineteen cases of upper gastrointestinal haemorrhage were seen during the study and 353 were shown to be bleeding from peptic ulcers. The exclusion of 4 who were not resuscitated because of serious concurrent disease and 71 who had been randomly allocated to treatment under the aggressive surgical policy left 278 cases for consideration, among whom the mortality was 4·7 per cent. Further haemorrhage occurred in 74 patients, of whom 12 died (16 per cent). The mortality among 204 patients who did not have further haemorrhage was 0·5 per cent ($\chi^2 = 26{\cdot}3$, $P < 0{\cdot}0001$).

The categorical variables which showed a significant association with further haemorrhage are listed in *Table 2*. The median values of the continuous variables which showed significant differences between patients with further haemorrhage and those without are listed in *Table 3*.

One hundred and sixteen patients (42 per cent) had the major endoscopic stigmata of haemorrhage and 53 per cent of these rebled. Amongst patients without stigmata, 8·5 per cent rebled ($\chi^2 = 66{\cdot}7$, $P < 0{\cdot}0001$). The presence of the major stigmata predicted further bleeding with a sensitivity of 82 per cent and a specificity of 72 per cent.

Stepwise logistical regression analysis using 75 per cent of the cases generated a formula for the probability that a patient would have further bleeding (*P*) incorporating six variables (age, history of previous ulcer surgery, haemoglobin concentration, the presence of a gastric ulcer, the major stigmata and concurrent illness). Maximum separation of patients with further haemorrhage from those without occurred using a cut-off point of $P = 0{\cdot}2$. Validation of the formula using the remaining 25 per cent of cases showed it to predict further haemorrhage with a sensitivity of 78 per cent and a specificity of 76 per cent. Sixty-two per cent of patients in the high risk group had further bleeding (*Table 4*).

As the presence of the major stigmata predicted further haemorrhage with high sensitivity but a high false-positive rate, a further analysis was done in order to derive a formula capable of identifying patients with stigmata who are unlikely to rebleed. This analysis generated a different formula:

$$\ln\left(\frac{P}{1-P}\right) = 0{\cdot}05\ (\text{age}) + 0{\cdot}66\ (\text{previous surgery}) + 0{\cdot}25\ (\text{haemoglobin}) + 0{\cdot}71\ (\text{units transfused}) - 9{\cdot}2$$

Definitions of the variables appearing in this formula are set out in *Table 5*, categorical variables being coded +1 when present and −1 when absent.

Maximum separation of patients with and without further haemorrhage again occurred using a cut-off point of $P = 0{\cdot}2$. As $\ln(P/1-P)$ when $P = 0{\cdot}2$ is $-1{\cdot}4$, the formula could be simplified for clinical use:

$$\frac{\text{age}}{20} + \frac{2\ (\text{previous surgery})}{3} + \frac{\text{haemoglobin}}{4} + \frac{7\ (\text{units transfused})}{10} > 7{\cdot}8$$

Table 3 *Continuous variables showing significant differences between patients with and without further haemorrhage (FH) (Mann–Whitney* U *test)*

Variable	Median value (range) FH		No FH		P
Age	67	(24–99)	60	(16–92)	< 0·005
BP systolic	112	(40–200)	120	(60–210)	< 0·0002
BP diastolic	70	(20–140)	79	(20–140)	< 0·02
Shock index*	0·87	(0·1–2·5)	0·77	(0·42–2·33)	< 0·0003
Haemoglobin	9·7	(3·8–14·1)	10·9	(4·2–17·0)	< 0·0004
Units transfused	6	(0–32)	3	(0–8)	< 0·0001

* Shock index = pulse/systolic BP

Table 4 *Sensitivity, specificity and accuracy of prediction of further haemorrhage using three different definitions of high risk*

	Stigmata	First equation (6 variables)	Second equation + stigmata
Sensitivity (%)	82	78	70
Specificity (%)	72	76	93
Accuracy (%)*	53	62	84

* Accuracy = proportion of patients in high risk group experiencing further haemorrhage

Table 5 *Definitions of variables used in the regression equation*

Variable	Definition
Age	Age of patient in years
Previous operation	History of previous surgery for peptic ulcer
Haemoglobin	Haemoglobin on admission (g/dl)
Units transfused	Units of blood/colloid for initial resuscitation

The high risk group was then defined as comprising those patients with the major stigmata who also satisfied the above formula. When this definition was applied to the independent group of patients, 84 per cent of those classifed as being at high risk were found to have rebled, justifying early surgery in all such patients. The predictions had a sensitivity of 70 per cent and a specificity of 93 per cent. Of the seven patients who had had further haemorrhage who were not identified as being at high risk, none had rebled massively, five had not required emergency operations and three had not been transfused.

A policy of early surgery in all patients identified as being at high risk would have led to an operation rate of 28 per cent in the series, whereas the actual rate was 36 per cent, and operating on all patients with stigmata would have resulted in an operation rate of 42 per cent. Early surgery in all high risk patients, before the onset of recurrent haemorrhage, would have reduced the incidence of rebleeding from 33 per cent to 10 per cent.

Discussion

Many previous studies have identified individual clinical variables which are significantly correlated with outcome following upper gastrointestinal haemorrhage. Most of these analyses have been concerned with death rather than further haemorrhage and have included all patients with haematemesis or melaena rather than being confined to ulcer patients. Although early diagnosis of the source of haemorrhage has not been shown to reduce mortality *per se*[8,9], the natural histories of bleeding from ulcers, varices, malignancies and other lesions are so different that accurate prediction of outcome demands an early and accurate diagnosis.

The ultimate aim of surgery in peptic ulcer haemorrhage is to prevent death from bleeding and a means of identifying which patients are likely to suffer further haemorrhage is a prerequisite to the appropriate use of surgery. Although stepwise logistical regression analysis is capable of generating a formula for the probability of a fatal outcome in any given patient, prediction of death is less useful than prediction of further haemorrhage as it does not aid clinical decision making. Many patients die of complications which are not surgically remediable, often without rebleeding[10]. Identification of patients at high risk for further haemorrhage, on the other hand, enables rebleeding to be averted through early surgical intervention.

Of the individual risk factors for further haemorrhage identified in the present study, an age of 60 years or more has long been regarded as carrying an increased risk of further haemorrhage[11], although Northfield did not find such an association in his series of patients[12]. The presence of shock was also associated with rebleeding, confirming the findings of Bornman *et al.*[13]. A low haemoglobin, a gastric rather than a duodenal ulcer and recent regular medication have not previously been identified as risk factors for rebleeding. As in previous studies, the major stigmata proved to have the greatest individual predictive value (*Table 2*).

Individually, the continuous variables have little predictive value because the differences in median values, although statistically highly significant, are small and the range of values is wide. It is noteworthy, however, that five of the six continuous variables which showed significant differences between those with further haemorrhage and those without, are indicators of the severity of the initial haemorrhage, implying that patients with large first bleeds have a high risk of rebleeding. The equation generated by stepwise logistical regression analysis enables these variables to be brought into consideration in calculating the likelihood of further haemorrhage.

When all variables were used in the regression analysis, the regression equation proved to be slightly more accurate than stigmata alone in predicting further haemorrhage (62 per cent as opposed to 53 per cent). Although the use of this formula to direct surgical intervention would have resulted in 19 per cent fewer unnecessary operations, this is a modest gain from a cumbersome formula. The analytical approach was therefore changed to one which sought to utilize the high sensitivity of the major stigmata in identifying patients who would rebleed, while refining the accuracy of the prediction.

The formula generated by this second analysis, when taken in conjunction with the presence of the major stigmata, predicted further haemorrhage with an accuracy of 84 per cent. Such accuracy justifies surgical intervention in all patients who fall into the high risk group ($P > 0{\cdot}2$ and stigmata present). This accuracy is bought at the price of a reduced sensitivity and 30 per cent of those who, in fact, rebled did not fulfil the criteria for the high risk group. It is noteworthy, however, that five of the seven patients classified as being at low risk who rebled did not require emergency operations and three were not transfused; failure to identify such patients is unlikely to lead to preventable deaths.

A policy of surgical intervention in all patients classified as being at high risk would have led to an operation rate of 28 per cent in the entire series, whereas the actual rate was 36 per cent and a policy of operating on all patients with the major stigmata would have resulted in 42 per cent of patients having operations. Operation rates of up to 43 per cent have been reported in recent papers[8–14] and a substantial number of these operations must have been done in patients who would not have rebled if treated conservatively. Selection of patients for surgery using the criteria set out above would greatly reduce the number of unnecessary operations, yet might enable two-thirds of all episodes of further haemorrhage to be averted, including all those of a serious nature. Given the strong association between further haemorrhage and a fatal outcome, it is difficult to believe that this would not have a beneficial effect on mortality.

Although the regression equation at first sight appears to be complex, it can be applied in clinical practice in its simplified form with relative ease. High risk patients are those with the major stigmata in whom

$$\frac{\text{age}}{20} + \frac{2\,(\text{previous surgery})}{3} + \frac{\text{haemoglobin}}{4} + \frac{7\,(\text{units transfused})}{10} > 7{\cdot}8$$

This calculation can be done manually or with a pocket calculator.

A limitation on the usefulness of formulae derived from a single series of patients is that they tend to reflect peculiarities and chance variations in the study population and thus require validation in other series of patients before they can command widespread acceptance. This problem has been partly avoided in the present study by deriving the formula using a randomly selected 75 per cent of the cases and validating it against the remaining 25 per cent. Even so, it may reflect peculiarities of Birmingham patients and further validation in other centres would be desirable. Final acceptance must, however, be based on a further clinical trial comparing the mortality among patients managed under established surgical guidelines with that resulting from the proposed new classification.

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Effect of the pre-operative response to H_2 receptor antagonists on the outcome of highly selective vagotomy for duodenal ulcer

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From 1979 to 1984, 141 consecutive patients (110 men, 31 women) underwent highly selective vagotomy (HSV) for duodenal ulcer (DU). All patients had received pre-operative treatment with full dose H_2 receptor antagonists (H_2RA). Indications for surgery were: persistent relapse on withdrawal of H_2RA, 107 (75·9 per cent); no response to H_2RA, 30 (21·3 per cent); intolerance of H_2RA, 1 (0·7 per cent); acute DU bleed, 2 (1·4 per cent); duodenal stenosis, 1 (0·7 per cent). Follow-up with a median of 47 months (24–85 months) revealed six patients (4·4 per cent) with endoscopically proven recurrence, three of whom were on non-steroidal anti-inflammatory drugs (NSAIDs). Only one patient with recurrent DU was a non-responder to H_2RA pre-operatively. Twenty-five patients remained symptomatic after HSV without ulcer recurrence, of which a highly significant proportion (41 per cent) were non-responders ($P<0·001$). The pre-operative response to H_2RA does not indicate the likelihood of ulcer recurrence after HSV. However, non-responders are more likely to continue with dyspeptic symptoms despite the successful healing of their ulcers. The DU recurrence rate in patients taking long-term NSAIDs is disappointingly high (33 per cent), putting the use of HSV in these patients into question.

Keywords: Highly selective vagotomy, H_2 receptor antagonists, recurrent duodenal ulcer

Highly selective vagotomy (HSV) has gradually become an accepted elective surgical treatment of duodenal ulcer (DU). Its recurrence rate is reported to be higher than that of classical ulcer surgery[1,2] but it has the advantage of a very low postoperative morbidity[3–5].

H_2 receptor antagonists (H_2RA) are now so widely used that all patients referred for elective DU surgery have received at least one or, more often, multiple courses of these drugs. Healing rates of 95 per cent after 2 months of treatment are reported[6], but on withdrawal of H_2RA the majority of patients will relapse (up to 85 per cent) in the first year[7]. These relapsing responders to H_2RA do well after HSV[8]; however, the position of HSV in the treatment of patients who fail to respond to H_2RA therapy is unclear. Blackett and Johnston[9] were initially enthusiastic, but a recent study from the same unit now suggests an unacceptably high recurrence rate (40 per cent) in this group[10], a view which is supported by Bardhan in a few selected patients[11]. This uncertainty led us to review our own results of HSV in this group of patients whose response to H_2RA was known before surgery.

Patients and methods

A retrospective study with up-to-date assessment was undertaken of all patients with an endoscopically proven DU treated by HSV in the University Surgical Unit from 1979 to 1984. All patients had been treated primarily with full dose H_2RA and were only referred for surgery after medical management failed to control their ulcers and symptoms. The case notes of all patients were reviewed and the pre-operative response to H_2RA was established from the endoscopy reports and outpatient enquiries. Two levels of H_2RA response were recognized: (i) 'relapsing responders', i.e. patients whose ulcers and symptoms responded to H_2 blockers but recurred some time after completion of the treatment; (ii) 'non-responders', i.e. patients whose ulcers and symptoms were unrelieved by full dose H_2 blockers.

A full history including patients' other drug treatments and smoking habits was taken, and information about postoperative symptoms was brought up to date by contacting the patient either by postal questionnaire, personal or telephone interview. This was carried out by a surgeon not involved in any of the operations. All patients who remained symptomatic after HSV were regastroscoped, but asymptomatic patients were not re-endoscoped after surgery.

HSV was carried out by consultants, senior registrars or lecturer grade surgeons, using the operative technique described by Johnson[12]. A Grassi intra-operative test for completeness of vagotomy was performed on a randomly selected group of patients using the method described by Grassi in 1971[13]. Pre-operatively a pentagastrin test was carried out using the method of Baron[14], but the results were not used for patient selection for either operation or whether a Grassi test should be performed.

All patient information was stored on an IBM PC-AT using dBASE III plus (Ashton-Tate) relational database. Statistical analysis was by the University of Sheffield IBM 3083 Mainframe Computer using the Minitab statistical package (Pennsylvania State University).

Results

From 1979 to 1984, 141 consecutive patients underwent HSV, 110 men and 31 women with a mean age of 43·3 years (range 18–77). The indications for surgical treatment are shown in *Table 1*.

The two major groups of relapsing responders and non-responders were compared, but no relationship to age, smoking habit, acid secretion or drug consumption to pre-operative H_2RA response was found (*Table 2*). However, it was apparently sex-related with a higher proportion of women (*Table 3*) in the non-responding group ($\chi^2 = 10·32, P < 0·01$), but this finding should be viewed with caution because of the disparity between the numbers of men and women undergoing HSV.

Despite strenuous efforts, 5 patients were lost to follow-up, which left 136 patients (96·5 per cent) available for detailed

Table 1 *Indications for surgical treatment*

Indication for surgery	Patients
Relapsing responder H_2RA	107 (75·9%)
Non-responder H_2RA	30 (21·3%)
Intolerance of H_2RA	1 (0·7%)
Acute DU bleed	2 (1·4%)
Duodenal stenosis	1 (0·7%)
Total	141 (100%)

H_2RA, H_2 receptor antagonists; DU, duodenal ulcer

Table 2 *Acid secretion before operation*

	Relapsing responder	Non-responder
Basal acid output (mmol H^+/h)	6 (0–22)	3 (0–21)
Peak acid output (mmol H^+/h)	39 (14–69)	35 (18–68)

Values are medians with range given in parentheses

Table 3 *Sex and H_2 receptor antagonist response*

	Non-responder	Relapsing responder
Women ($n=30$)	43%*	57%
Men ($n=107$)	16%*	84%

* $\chi^2=10\cdot32$, $P<0\cdot01$

study, with a median time since operation of 47 months (range 24–85).

Recurrent ulcer

The patient review showed that 31 patients continued to suffer dyspeptic symptoms after HSV; all these patients were regastroscoped. This showed that six patients (4·4 per cent) had recurrence of their DU, the details of which are shown in *Table 4*. In the other 25 patients (18·4 per cent) with continuing symptoms, their ulcers had healed. Only one of the six patients with recurrent DU was a non-responder pre-operatively, the rest being relapsing responders; this ratio is similar to that in the whole study group ($\chi^2=0\cdot1$, n.s.).

Half the recurrent DU occurred in patients taking regular NSAIDs; there were nine such patients in the study group, three of whom suffered a recurrence. Regular NSAIDs therefore significantly increased ulcer recurrence after HSV ($\chi^2=19\cdot12$, $P<0\cdot001$). Of the 25 patients who remained symptomatic without recurrence (*Table 5*), we see that 41 per cent of non-responders compared with only 13 per cent of relapsing responders remained symptomatic; this difference is highly significant ($\chi^2=12\cdot91$, $P<0\cdot001$).

Grassi test

A Grassi intra-operative test was performed in 34 patients who were well matched (*Table 6*) with the 102 other study patients, except for their anti-inflammatory drug consumption. The test was carried out when the surgeon was satisfied that he had denervated the parietal cell area. However, only 14 patients (41 per cent) had complete vagotomies at the first attempt and a further 14 were made complete by further vagal dissection, but in 6 patients there was still a small area of acid mucosa despite maximal vagal division.

Mortality and morbidity

There was no operative mortality but two patients died at 3 years and 4 years postoperatively from unrelated causes. The 30-day postoperative morbidity was as follows: wound infection rate of 11·7 per cent in patients undergoing a gastrotomy as part of a Grassi test, compared with 5·9 per cent in the non-Grassi group (prophylactic antibiotics were not used) ($\chi^2=1\cdot3$, n.s.). Despite routine use of subcutaneous heparin prophylaxis, two patients developed deep venous thrombosis and a further patient suffered a pulmonary embolus.

Discussion

This study again confirms HSV to be an effective, safe treatment for DU. Our low recurrence rate may in part be attributable to the precise operative technique, with special reference being made to the length of antrum left innervated (<6·0 cm).

This study shows that recurrent DU can occur late (after 5 years); therefore we may have to adjust our recurrence rate with the passage of time. Interestingly, none of the recurrent ulcers occurred in patients who had a Grassi test, even those who remained positive over a small area after HSV. However, 41 per cent of the Grassi group initially had a positive test and only became negative after further dissection. Although this suggests that the further vagal division directed by the Grassi test prevented recurrence, no significant difference in recurrence rate could be shown, owing to the small number of recurrent ulcers in the non-Grassi group (χ^2 with Yates's correction. Also, none of the Grassi test patients were taking regular NSAIDs compared with nine patients in the rest of the study group who

Table 4 *Recurrent duodenal ulcer*

Sex	Age	H_2RA	Recurrence time (months)	Smoker	Drug
M	23	Non-responder	14	Yes	No
M	24	Relapsing responder	12	No	No
M	51	Relapsing responder	26	No	No
M	57	Relapsing responder	48	Yes	NSAID
F	53	Relapsing responder	67	Yes	NSAID
F	68	Relapsing responder	39	No	NSAID

NSAID, non-steroidal anti-inflammatory drug

Table 5 *H_2RA response and postoperative symptoms*

	Symptomatic ($n=25$)	Non-symptomatic ($n=107$)
Non-responder ($n=29$)	41%*	59%
Relapsing responder ($n=103$)	13%*	87%

* $\chi^2=12\cdot9$, $P<0\cdot001$

Table 6 *Grassi test to assess completeness of vagotomy*

	Grassi ($n=34$)	Non-Grassi ($n=102$)
Male	75%	79%
Female	25%	21%
Mean age	43 years	44 years
Smokers	58%	48%
Relapsing responders	83%	73%
Non-responders	17%	23%
Pre-operative BAO (mmol H^+/h)	4 (0–21)*	5 (0–22)*
Pre-operative PAO (mmol H^+/h)	42 (18–66)*	37 (14–69)*
Anti-inflammatory drugs	0	9

* Median value, range given in parentheses
BAO, basal acid output; PAO, peak acid output

were, and this has been shown to be a most potent cause of recurrent DU after HSV.

Five of the six patients with recurrent DU had their ulcers healed using full dose H_2RA for 6 weeks and remained symptom-free on maintenance therapy. This includes the patient who did not respond to H_2RA before his HSV. The remaining patient whose recurrence was a pyloric canal ulcer was treated by antrectomy without further vagotomy and remains symptom-free.

HSV was successful in healing 95 per cent of DU, but some of these patients persisted with dyspeptic symptoms postoperatively. Failure of symptom control was more common amongst patients who failed to respond to H_2RA pre-operatively. We therefore now warn non-responders that, although we can heal their ulcers by HSV, removing the risk of complications, they may continue with postoperative dyspepsia. Possible explanations for this are: (1) that the patient may be having transient episodes of ulceration which are not being identified on repeat endoscopy, but this seems unlikely as the patients who remained symptomatic in the Grassi group all had a satisfactory reduction in acid secretion after HSV[15]; (2) that the symptoms and DU were secondary to a gastroduodenal motility disorder[16,17] and therefore healing the ulcer did nothing for the primary problem; (3) that the presence of an ulcer crater is not a necessary prerequisite for 'ulcer' symptoms; (4) that the symptoms were due to a second unrelated pathology. Further work is required before the correct explanation for this interesting group of patients can be found.

In conclusion, the results of this study indicate that the patient's pre-operative response to H_2RA does not indicate the likelihood of ulcer recurrence after HSV; that patients taking regular NSAIDs have a significantly increased chance of suffering an ulcer recurrence after HSV; and that a patient who fails to respond to H_2RA pre-operatively is more likely to remain symptomatic without ulcer recurrence postoperatively.

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Gastric emptying and clinical outcome after Roux-en-Y diversion

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The results of 48 Roux-en-Y (RY) diversion procedures are reported: 41 were performed as secondary procedures and 7 as part of a primary operation for peptic ulcer. There was no operative mortality, but four patients developed temporary fistulae in the postoperative period and three patients required reoperation. Good clinical results were found when RY diversion was performed as a primary procedure or when the indication for operation was peptic ulceration. The overall results, however, were poor: 24 patients (50 per cent) felt that they had not benefited and 32 patients (67 per cent) remained in Visick grades III or IV. The main cause of failure was gastric stasis, especially of solid food. Gastric emptying studies were carried out after RY diversion in 22 patients, most of whom had symptoms of stasis. Emptying of liquids was found to be normal in most patients, but emptying of solids was delayed, the median $t_{\frac{1}{2}}$ for solids being 160 (75–370) min compared with 67 (50–85) min in DU patients. Bilious vomiting improved significantly after RY diversion, but 18 patients (38 per cent) complained of vomiting food and 32 patients (67 per cent) experienced postprandial distress or pain. Loss of the antral mill, vagotomy of the gastric remnant and, perhaps, resistance to gastric emptying by the Roux loop itself may together explain the delay in gastric emptying of solids after RY diversion.

Keywords: Alkaline reflux gastritis, Roux-en-Y diversion, gastric emptying

Excessive reflux of duodenal or jejunal content into the stomach is common after both partial gastrectomy (PG) and vagotomy with a drainage procedure (V+D). Though many patients remain asymptomatic in spite of such reflux, others develop symptoms such as epigastric pain, nausea and bilious vomiting[1–4]. Roux-en-Y (RY) diversion, first described by Roux in 1897[5], is still widely used in the treatment of bilious vomiting after PG or V+D, and has been reported to yield good results, provided that the diverting loop of jejunum is 40–50 cm long[6–8].

It is somewhat unusual, however, for bilious vomiting to occur as an isolated symptom. More often, patients who require revisional surgery after PG or V+D complain of several symptoms, some of which may be unrelated to enterogastric reflux. Our impression at a gastric follow-up clinic was that, though successful in relieving bilious vomiting, RY diversion often yielded disappointing results. In particular, symptoms suggestive of impaired gastric emptying, such as pain or bloating after meals, nausea and vomiting, seemed to be common sequelae. We wondered whether RY diversion was solving one clinical problem at the price of creating other problems. For that reason, we reviewed the outcome of RY diversion in 48 patients, 22 of whom also underwent tests of gastric emptying.

Patients and methods

Patients

Forty-eight patients underwent RY diversion between 1975 and 1986. Many of them had been referred from elsewhere as failures of gastric surgery. There were 23 men and 25 women, aged from 35 to 75 years (median, 50 years). In 22 patients this was the first reoperation, but 19 patients had undergone 2 or more previous gastric operations (*Table 1*). In seven patients, RY diversion formed part of a primary operative procedure. The median interval between the first operation and RY diversion was 9 years (interquartile range 4–15 years).

Diagnosis

Before RY diversion was undertaken, a precise diagnosis of the cause of the patient's symptoms was sought by means of the history and endoscopic, radiological and gastric emptying studies. The indications for RY diversion (*Table 1*) were, predominantly, enterogastric reflux in 28 patients, gastric stasis in 7 and peptic ulceration in 13. Many patients, however, had a variety of symptoms such as pain, nausea, dumping and diarrhoea, such that the neat classification into three groups is somewhat arbitrary. Patients diagnosed as having enterogastric reflux had both the macroscopic appearances of biliary gastritis at endoscopy and the microscopic features of the condition[9]. Patients with gastric stasis had been found to have food residues in the stomach at endoscopy after an overnight fast, and gastric emptying studies showed delayed emptying. The 13 patients with peptic ulceration comprised 3 patients with pyloric stenosis, 3 with combined prepyloric and duodenal ulceration and 7 with recurrent peptic ulceration after V+D or PG.

Operative procedure

Most of the operations were performed by the senior author or his senior registrar. The operative procedure itself usually consisted of a truncal vagotomy with antrectomy, closure of the duodenal stump and formation of a 50 cm RY loop of jejunum, which was anastomosed to the gastric remnant. In most cases an antecolic anastomosis was fashioned using two layers of continuous chromic catgut and the efferent loop sutured to the greater curve. Normally the whole width of the stomach was used to provide a wide stoma. Thirty patients had previously undergone vagotomy (including four who had undergone revagotomy) and six patients had a primary vagotomy added to the RY procedure. Twelve patients did not undergo vagotomy, either at the initial operation or at the time of RY diversion. The antrectomy was relatively conservative, the mean weight of the resected gastric antrum in 15 patients being only 73 g (35–150 g): thus, a relatively large gastric remnant was left behind.

Assessment of results

Clinical results. Patients were reviewed annually at a gastric follow-up clinic, where they were interviewed by a physician and surgeon who did not know what type of operation had been performed. The duration of follow-up after RY diversion ranged from 4 to 132 months, with a mean and median of 26 and 24 months, respectively. The duration of follow-up after the first gastric operation was obviously much longer, except in patients who underwent RY diversion as a primary procedure. Individual symptoms were recorded and the patient's overall state graded according to the modified Visick classification. The symptoms and Visick status at most recent follow-up were compared with the

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Table 1 *Indication for Roux-en-Y diversion procedure in 48 patients with details of previous operations*

Indication	Number of patients	Roux-en-Y as primary or revisional procedure	Nature of previous operations: Vagotomy	Vagotomy + partial gastrectomy	Partial gastrectomy
Enterogastric reflux	28	Primary 2*			
		Revisional 26	12	4	10
Gastric stasis	7	Primary 0			
		Revisional 7	5	2	0
Primary or recurrent peptic ulceration ± pyloric stenosis	13	Primary 5			
		Revisional 8	7	0	1

* These patients had previously undergone cholecystectomy

Table 2 *Patients' symptoms before and after Roux-en-Y diversion*

Group	Number of patients	Vomiting: All types	Bile	Food	Postprandial distress or fullness	Epigastric pain	Nausea	Gastro-oesophageal reflux or heartburn
Group 1								
Enterogastric reflux	28							
Before RY		20	20*	3	7	25	22	15
After RY		10	5	9	20	18	17	10
Group 2								
Gastric stasis	7							
Before RY		6	2	5	5	5	7	7
After RY		5	3	5	5	5	4	1
Group 3								
Peptic ulceration	13							
Before RY		6	3	5	4	12	10	7
After RY		4	1	4	7	4	4	2
Total	48							
Before RY		32	25*	13	16	42	39	29*
After RY		19	9	18	32	27	25	13

* Significant difference $P<0\cdot001$

patient's symptoms and Visick grade before RY diversion. Each patient was asked whether or not the operation had been beneficial. Endoscopy was performed if the patient was symptomatic to exclude recurrent ulceration or stenosis at the stoma.

Gastric emptying studies. Twenty-two patients underwent detailed studies of gastric emptying after RY diversion. They were not representative of the entire group of 48 patients, since most of them (19 of 22) were suffering from troublesome symptoms such as vomiting, pain and postprandial satiety and were regarded as having a poor result after RY diversion (Visick grades III or IV).

The studies were carried out in the Department of Nuclear Medicine using technetium, ^{99m}Tc, labelled liquid and solid meals. Serial images were obtained using a gamma camera (Elscint Dymax LF, Berinsfield, Oxfordshire, UK) interfaced to a digital computer (Digital Equipment Corporation, Reading, UK, PDP-11. In the studies of emptying of liquids, the patient drank 200 ml of water to which was added 10 MBq of ^{99m}Tc-DTPA. Thirty frames, each of 1 min duration, were acquired. Using a region of interest over the stomach, seen on early frames, an activity–time curve was generated. One hour after completion of the liquid meal, the patient ate a solid meal consisting of one scrambled egg on two rounds of toast with 25 g of butter and a cup (150 ml) of tea. During cooking 10 MBq of ^{99m}Tc labelled macro-aggregated albumen was added to the egg. Thirty 1 min frames were acquired from the beginning of the meal and activity–time curves generated. A further 30 min of data were acquired ('late phase') beginning 1 hour after the start of the meal. The liquid and late phase solid emptying curves were both assumed to be mono-exponential and, using a curve fitting routine, the times taken for half the meal to leave the stomach ($t_{\frac{1}{2}}$) were calculated.

Statistical analysis. Results were analysed by the Mann–Whitney U test and χ^2 test, with Yates's correction where necessary.

Results

Operative mortality

There was no operative mortality. One patient has since died of cerebral haemorrhage.

Postoperative morbidity

Eight patients developed specific complications of the RY diversion. Two patients suffered significant haemorrhage from the suture line, one requiring reoperation. Two patients were shown to have a physical obstruction at the gastrojejunal anastomosis which required refashioning. Three patients developed an upper gastrointestinal fistula and one a faecal fistula but all eventually closed with conservative management.

Functional results (*Table 2*)

In group 1 patients with enterogastric reflux (28 patients), bilious vomiting improved significantly after operation ($P<0\cdot001$), though five patients still experienced this symptom to a lesser degree. Other symptoms, however, were not improved. In particular, symptoms suggestive of gastric stasis such as food vomiting, postprandial fullness, epigastric pain and nausea were all common. In addition, 16 patients complained of inability to eat a normal sized meal.

Group 2 patients with gastric stasis (7 patients) showed no significant improvement in their symptoms after RY diversion.

In group 3 patients with peptic ulceration (13 patients), symtoms improved after RY diversion through several still

Table 3 *Results of Roux-en-Y diversion expressed according to the Visick classification*

Group	Number of patients	Pre-operative Visick grade I	II	III	IV	Postoperative Visick grade I	II	III	IV
Group 1 Enterogastric reflux	28	0	0	8	20	5	3	8	12
Group 2 Gastric stasis	7	0	0	1	6	1	1	1	4
Group 3 Peptic ulceration	13	0	0	0	13	2	4	6	1
Total	48	0	0	9	39	8	8	15	17

The pre-operative Visick grade is indicated

Table 4 *Patients' assesment of the outcome of Roux-en-Y diversion*

Group	Number of patients	Improved	Not improved
Group 1 Enterogastric reflux	28	10 (36)	18 (64)
Group 2 Gastric stasis	7	2 (29)	5 (71)
Group 3 Peptic ulceration	13	12 (92)	1 (8)
Total	48	24 (50)	24 (50)

Numbers in parentheses are percentages

experienced some symptoms, particularly postprandial fullness and food vomiting.

When the 48 patients were considered together, symptoms of heartburn or reflux improved significantly after RY diversion. Although there was a reduction in the number of patients with vomiting, enquiry as to the type of vomiting revealed a significant improvement in bilious vomiting but food vomiting became more common. More patients complained of postprandial fullness after operation and many patients continued to complain of epigastric pain and nausea. Food vomiting, postprandial fullness, epigastric pain and nausea are all symptoms suggestive of gastric stasis and usually occur in combination. Thirty-five patients (73 per cent) from the series had one or more of these symptoms after RY diversion and twenty-three patients (48 per cent) complained of having to limit the size of their meals.

Visick grades (Table 3)

Pre-operatively, 39 patients were classified Visick grade IV and 9 patients were classified Visick grade III. After RY diversion, 17 patients (35 per cent) were classified as having a Visick grade IV result and 32 patients (67 per cent) were in Visick grades III or IV. Good results, however, were obtained by the 13 patients in group 3, the peptic ulcer group, only 1 of whom was in Visick grade IV; in contrast, 12 of 28 patients in group 1 ($P<0{\cdot}05$) and 4 of 7 patients in group 2 were in Visick grade IV.

The Visick grade 6 months after operation was compared with the Visick grade at the most recent visit to the clinic. Symptoms were found to have worsened in 12 patients and improved in 5 patients. Overall, when the final outcome was compared with the result recorded during the first year after RY diversion, no evidence of significant change in the patients' functional results was found.

Results of RY diversion as a primary and as a revisional procedure

Only 1 of the 7 patients who underwent RY diversion as the primary operative procedure had a poor, Visick grade IV, result, whereas 16 of 41 patients who underwent RY as a revisional procedure had a poor result.

RY diversion with and without vagotomy compared

When the outcome according to the Visick classification was compared in these two groups, there was no evidence that addition of vagotomy improved, or worsened, the clinical result. None of the 12 patients without vagotomy developed recurrent ulceration; one of the vagotomized patients developed a recurrent, stomal ulcer.

Patients' opinion

Of the 48 patients, 24 (50 per cent) felt that they had been improved by RY diversion (*Table 4*). Of the 13 patients in group 3, 12 considered that they had been improved by the operation, whereas only 12 of the remaining 35 patients felt that they had been improved.

Gastric emptying studies

Solid food. The median $t_{\frac{1}{2}}$ (interquartile range) for solids was 160 (75–370) min after RY diversion, compared with 67 (50–85) min in control (DU) patients ($P<0{\cdot}01$) (*Figure* 1). Of the 22 studies, 15 showed delayed gastric emptying of solids, and 14 of these 15 patients complained of food vomiting and/or epigastric fullness. Five patients who had normal empyting of solids according to the results of the test nevertheless had symptoms suggestive of stasis; three patients complained of epigastric fullness alone, but two patients described food vomiting.

Five of the seven patients with pre-operative stasis were investigated by gastric emptying studies both before and after RY diversion. The rate of solid emptying slowed in three cases and improved in two cases.

Liquids. The median $t_{\frac{1}{2}}$ and interquartile range for liquids was 8·7 (3·3–18) min after RY diversion, and the results of most tests were within the normal range of $t_{\frac{1}{2}}$ (5–10 min) for this laboratory. However, 8 of the 22 studies showed delayed gastric emptying of liquids and each of these 8 patients had clinical symptoms of stasis and were in Visick grades III or IV.

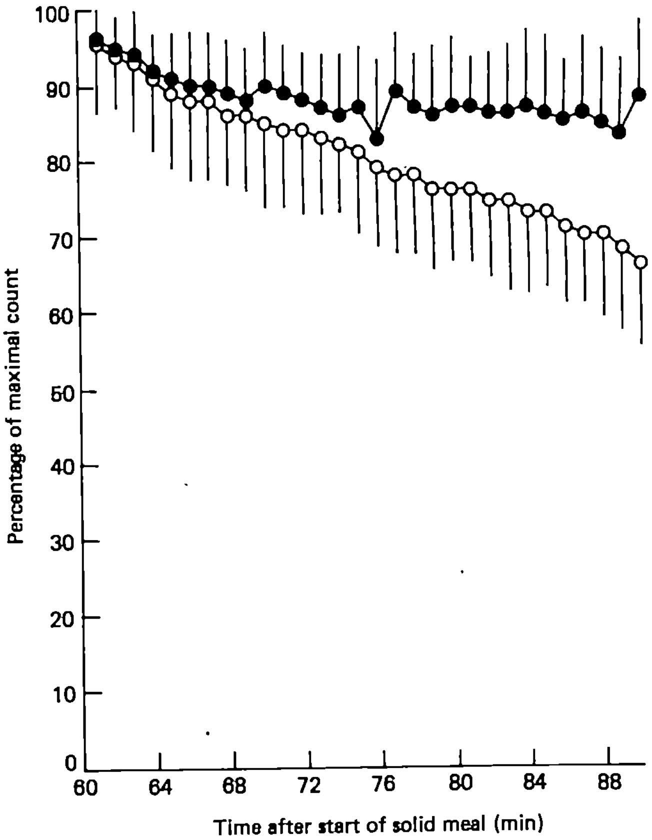

Figure 1 *Mean curves for the gastric emptying of a solid meal in patients with uncomplicated duodenal ulcer disease and in patients after Roux-en-Y diversion.* ●, *RY patients;* ○, *uncomplicated DU patients*

Discussion

The main findings were that, overall, the clinical results of RY diversion were poor: two-thirds of the 48 patients remained in Visick grades III or IV and only half the patients felt that they had benefited. Symptoms of bilious vomiting and heartburn or gastro-oesophageal reflux improved significantly, but nausea and epigastric pain did not, vomiting of food became more common, and postprandial discomfort or distress, which had been experienced by 16 patients (33 per cent) before reoperation, was experienced by 32 patients (67 per cent) after RY diversion. Neither the patients' symptoms nor their overall Visick grades improved with the passage of time after RY diversion.

Certain subgroups of patients, however, fared better than the average. Thus, five of the seven patients in whom RY diversion was performed as part of a primary operation for peptic ulcer obtained good results, and only one fared badly. Other authors have reported good results after vagotomy and antrectomy with RY reconstruction as a primary operation for duodenal ulcer[10–12]. We have also used the RY method of reconstruction as a primary procedure in 13 patients after subtotal gastrectomy for gastric carcinoma, and none of these patients had a bad, Visick grade IV, result. In this study, there were 13 patients who underwent RY diversion for peptic ulceration, whether primary or recurrent (group 3), and these patients did fairly well, only one having a bad result.

It was interesting that the addition of vagotomy, which is universally recommended, appeared to make no difference to the outcome. Indeed, the only patient to develop a recurrent (stomal) ulcer was in the group of patients who underwent vagotomy. However, the numbers of patients were too small and follow-up too short to permit definite conclusions.

Results were poor in the 41 patients who underwent RY diversion as a revisional procedure. Despite a significant improvement in bilious vomiting and in heartburn or reflux, most of these patients developed symptoms suggestive of gastric stasis (*Table 2*) and no fewer than 30 of them (73 per cent) had a poor functional result (Visick grades III or IV). These observations are in agreement with previous reports of a high incidence of gastric stasis after RY diversion[13–16].

The clinical evidence of gastric stasis after RY diversion was supported by the results of the gastric emptying studies, which showed, on average, normal emptying of liquids but slow gastric emptying of solids. Median $t_{\frac{1}{2}}$ for solids was 160 min after RY diversion, compared with 67 min in patients with duodenal ulcer before operation. These studies were admittedly carried out in the 19 patients with the worst symptoms of stasis (and in 3 other patients with mild symptoms) but the patients tested formed a high proportion, almost 50 per cent, of the 41 patients who underwent RY diversion as a revisional procedure. Some of the other patients might also have been found to have slow gastric emptying, had they been tested. An inadequate gastrojejunal stoma was excluded by endoscopy.

We believe that gastric stasis of solids after RY diversion is attributable to three factors: the antrectomy, the vagotomy, and the presence of the RY loop of jejunum. The gastric antral mill is responsible for grinding solid food into chyme, and its removal by antrectomy or partial gastrectomy may be expected to impair the breakdown of solid food into smaller particles. The addition of vagotomy will render the gastric remnant atonic, and thus less capable of expelling solid food into the jejunum. As Hocking *et al.* commented, 'a vagally denervated small gastric pouch (after RY) serves as an atonic reservoir which impairs the emptying of solids'[14]. This idea fits with our clinical observation at endoscopy that many of the patients still have food in the gastric remnant after an overnight fast. Although our results show that the addition of vagotomy makes no difference to outcome the numbers are too small to question this argument, particularly as we feel that vagotomy is only part of a multifactorial process responsible for stasis. Finally, studies in man[16] have shown that in the fasted state the migrating motor complex is either absent or disrupted in the Roux limb, and none of the seven subjects who were studied converted to a fed state after a solid meal. Hence, pain, nausea and vomiting after RY diversion may be secondary to a defect in motor function, the Roux limb acting as an area of functional obstruction.

Many authors who have studied the effects of 'remedial' operations in patients with side effects of gastric surgery have found that good results cannot be guaranteed. That has certainly been our own and others' experience with the RY procedure, though our results seem to be the worst ever reported after this operation. With the wisdom of hindsight, we think that several patients in this series were injudiciously selected for RY conversion. Some were polysymptomatic and somewhat neurotic, though whether the neurosis was secondary to the side effects of gastric surgery or preceded such surgery was unclear. Many patients evinced a variety of symptoms, and it was difficult to be certain that excessive reflux of 'bile' into the stomach was the principal defect. The use of an instillation test to infuse autologous enteric juices on to the gastric mucosa has been suggested as a possible way forward in the selection of patients for revisional surgery[17]. We did not attempt to quantify enterogastric reflux in any systematic fashion before the RY procedure, partly because the appropriate techniques were not available in the earlier years, and partly because of a certain scepticism about the clinical value of such measurements[18]. Certainly, many patients have copious reflux, but few symptoms.

If RY diversion yields such disappointing results, what can be done for patients such as those described in this paper? First, the problem should be kept to a minimum; most patients with duodenal or benign gastric ulceration can now be treated medically, without operation. If elective operation is indicated, use of highly selective vagotomy with preservation of the antral mill and pylorus will eliminate the problem of 'bile' reflux[19,20]. For patients who suffer from dumping and enterogastric reflux after vagotomy with a drainage procedure, closure of the gastro-enterostomy or reversal of the pyloroplasty is less dangerous than RY diversion and will slow gastric emptying and diminish reflux, though some patients will develop gastric retention. If bilious vomiting is the predominant side effect after partial gastrectomy, RY diversion will help many patients, but the potential benefit of adding a vagotomy of the gastric remnant must be weighed against the considerable risk that gastric stasis may ensue. For patients with severe stasis after vagotomy–antrectomy with RY reconstruction, a higher gastric resection may have to be considered, and indeed we have two patients whose symptoms were improved by total gastrectomy and a Roux link-up. These are extreme measures, however, and dangerous to life. The main lesson is that reflux of 'bile' into the stomach should be prevented.

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Importance of cellular DNA content in pre-malignant breast disease and pre-invasive carcinoma of the female breast

The risk of malignant change in pre-invasive breast disease such as proliferative atypia (PA) or the risk of invasive carcinoma arising from ductal carcinoma in situ *(DCIS) remains uncertain in individual women because of the absence of any prognostic criteria. In order to clarify this, the cellular DNA content (ploidy) of 51 screen-detected lesions has been investigated. Cellular DNA measurements were made by static cytometry following Feulgen staining of disaggregated tissue sections and the resulting histograms classified as either diploid or aneuploid. Thirteen cases of PA and twelve of DCIS were compared with twenty-six biopsies showing DCIS with adjacent invasive carcinoma (DCIS + Ca). In the latter group, ploidy of the invasive carcinoma was compared with the associated DCIS in 16 cases. Aneuploid cells were found in approximately 30 per cent of PA and DCIS lesions but in 23 of 26 cases of DCIS + Ca. Of 16 assessable cases of co-existing DCIS and micro-invasive carcinoma both were aneuploid in 11, both diploid in 1, and in 4 cases the DCIS was aneuploid whereas the invasive carcinoma was diploid. These results suggest that aneuploidy may be of value in predicting the most biologically aggressive of these pre-invasive lesions.*

Keywords: DNA content, premalignant breast diease, pre-invasive carcinoma

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There is increasing evidence that screening asymptomatic women for breast cancer leads to a reduction in mortality[1,2] and this has given rise to public pressure to implement a national screening programme. However, as well as detecting early breast carcinoma, screening uncovers pre-invasive lesions, the natural history of which is uncertain. This has led to difficulties in determining a logical management policy for the increasing number of patients detected with *in situ* carcinoma of the breast[3].

Retrospective studies suggest that up to one-third of women with *in situ* carcinoma treated by excision biopsy will go on to develop invasive carcinoma[4] and there are no morphological features which will differentiate these lesions from those that do not recur. A method of selecting progressive disease would therefore be of importance, because local treatment of this lesion should result in cure, whereas inadequate therapy allows progression in some cases to invasive carcinoma, most of which will be incurable[5].

Cellular DNA content increases during malignant transformation due to enhanced proliferative activity and alteration in nuclear chromatin content. We have assessed the changes in pre-invasive breast lesions, proliferative atypia (PA) and ductal carcinoma *in situ* (DCIS) in an attempt to clarify which lesions are most at risk of invasion.

Patients and methods

Patients

Fifty-one asymptomatic women between the ages of 45 and 70 years with screen-detected breast lesions were studied. Thirteen of these had a histopathological diagnosis of PA, twelve of DCIS and twenty-six had DCIS associated with micro-invasive carcinoma (DCIS + Ca). Patients with micro-invasive carcinoma subsequently underwent mastectomy whereas those with proliferative atypia and DCIS without invasion were treated by wide excision. All histological examinations were carried out by one histopathologist (N.G.) experienced in the histopathological diagnosis of screen-detected breast lesions[3] and the exclusion of invasive carcinoma was made only after examination of multiple tissue blocks.

Preparation of cell suspensions

From each patient a diagnostic 5 μm histological section was taken from the tissue block prepared from the biopsy, stained with haematoxylin and eosin and areas of interest were mapped out on to the slide. A consecutive section 40 μm thick was then cut, followed by a further 5 μm section which was stained and examined histologically. The two histological slides were compared to ensure that the lesion identified in the first section was present throughout the full thickness of the 40 μm section. Areas of interest from the first slide, plotted on to the thick section, were microdissected from this section and disaggregated enzymatically in 0·5 per cent pepsin[6]. After resuspension in saline, 100 μl of the cell suspension was placed on a glass microscope slide pre-treated with poly-L-lysine (Sigma) and post-fixed in carbowax. Nuclei were stained using the Feulgen technique after hydrolysis with 5 M HCl at room temperature. After staining the preparations were passed through three changes of bisulphite water before being mounted in DPX.

DNA measurement

Measurements were made by means of a Vickers M85 scanning and integrating microdensitometer at 550 nm with a × 40 objective and scanning spot size of 0·5 μm in the plane of the specimen. A mask which had a diameter of either 10, 15 or 20 μm was used, depending on the size of the cells in the sample. The DNA content of 100 randomly chosen epithelial cells was measured, cells being selected using a grid system to prevent any bias and histograms of DNA content were plotted. Subsequently, the whole slide containing up to 2000 cells was scanned for the presence of hypertetraploid cells; the histograms were then amended and classified as either aneuploid or diploid. In preliminary experiments, comparing tissue from the same tissue block, the method was found to be reproducible for both aneuploid and diploid tumours and there was no interobserver variation.

Statistics

Ploidy variation was analysed using a χ^2 test employing a Yates's correction.

Results

Ploidy values were determined in 51 biopsies (*Table 1*) and 31 (60 per cent) were classified as aneuploid and the remainder as diploid. There was no relationship between ploidy status and

Table 1 *The ploidy status of the three pathological groups*

	Histological group		
Ploidy status	PA	DCIS	DCIS+Ca
Diploid	9	8	3
Aneuploid	4	4	23
Total	13	12	26

PA, proliferative atypia; DCIS, ductal carcinoma *in situ*; DCIS+Ca, DCIS associated with micro-invasive carcinoma

the morphological appearance, the size of the lesion or the patients' age or menopausal status.

In 12 cases in which DCIS lesions were found in isolation, 4 (33 per cent) were aneuploid. A similar distribution of cellular DNA content was found in the 13 biopsies of proliferative atypia, 4 being aneuploid. A difference was observed between these two groups and the cells of DCIS found in association with micro-invasive carcinoma. Twenty-three (90 per cent) of these twenty-six lesions were aneuploid, which was a significantly greater proportion than that observed in proliferative atypias ($\chi^2=9{\cdot}6$, $P<0{\cdot}001$) or isolated DCIS biopsies ($\chi^2=10{\cdot}9$, $P<0{\cdot}001$).

In order to ensure that the DCIS cell suspensions, from lesions where the DCIS occurred in the same field as invasive carcinoma, were not contaminated by these frankly malignant cells, the DCIS and the invasive elements were dissected free and processed separately. For 16 cases in which this was done the ploidy of each sample DCIS was then compared with its corresponding invasive element. In one case the DCIS and the malignant cells were both diploid and in eleven both elements were aneuploid. However, four (25 per cent) of the micro-invasive carcinomas contained only diploid cells, whereas their adjacent DCIS was aneuploid. It is therefore unlikely that the high proportion of aneuploidy in the DCIS of this subset was the result of including invasive cells in the cell suspension.

Discussion

Mortality benefit from screening programmes may be partly explained by the large numbers of pre-invasive lesions which are detected[3,7], as the detection of palpable invasive carcinoma is probably of limited benefit due to the early metastatic potential of breast carcinoma. Ductal carcinoma *in situ* is potentially curable but this is dependent on adequate local treatment[8]. Mastectomy will eradicate DCIS but not all lesions will be progressive and such a radical treatment is therefore not always necessary. Progressive and recurrent disease after inadequate local treatment may be associated with the development of invasive carcinoma[4] and an expectant management policy may lose the potential benefit of early detection by screening.

If the retrospective studies reflect the natural history of this condition, only a minority of patients will develop frank malignancy. A policy of aggressive therapy for all cases would lead to unnecessary mastectomy in up to 70 per cent of women. Other methods of treatment, such as radiotherapy or subcutaneous mastectomy, have been reported to be either ineffective or inadequate[9,10], which leaves two alternative treatments—local excision or mastectomy—the former being inadequate in 20–30 per cent of patients and the latter being unacceptably aggressive for the majority, especially when set against the increasing use of conservation surgery for invasive carcinoma. Attempts have been made to resolve this clinical dilemma by the use of morphological characteristics to determine which lesions will progress.

Andersen *et al.*[11] attribute prognostic significance to the morphological pattern of DCIS within the breast describing microfocal, diffuse and tumour forming varieties which includes comedo carcinoma. Carter and Smith[12] and Lagios *et al.*[13] both found an increased risk of micro-invasion of DCIS larger than 25 mm, although we have not confirmed this in the present study. Electron microscopy studies have shown that there may be evidence of invasion in lesions where there is no breach of the basement membrane as assessed by light microscopy, but this is ony available as a routine in relatively few pathology departments. Wellings *et al.*[14] have proposed a spectrum of lesions which progress from proliferation to atypical proliferation before the development of invasive carcinoma based on the examination of cancer-associated and non-cancer-associated breasts. DuPont and Page[15] have recently reported a large series of women who have had breast biopsies showing features of atypical proliferation and who progressed to invasive carcinoma, and have assigned risk to women with such lesions varying form four to five times that of the general population.

In this investigation we have found aneuploid cells and consequently a high risk of developing invasive carcinoma in both DCIS and proliferative atypia. In DCIS associated with micro-invasion the majority of the lesions were aneuploid even though a quarter of the associated invasive lesions were diploid. Similar variation in cellular chromatin content has been found in the atypical hyperplastic lesion and carcinoma *in situ* of the cervix uteri[16]. This has also previously been described in a small number of patients with benign breast disease[17,18] and in four of these women whose biopsies contained aneuploid cells invasive carcinoma subsequently developed. This would support our hypothesis that aneuploid lesions of the breast are at high risk of progressing to invasive carcinoma and the cellular DNA content could form the basis of a prognostic index for the assessment of pre-invasive breast disease.

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Multicentre clinical trial of low volume fresh frozen plasma therapy in acute pancreatitis

Fresh frozen plasma (FFP) has been proposed as a specific therapy for acute pancreatitis. Reduced mortality encountered in an uncontrolled clinical study and a controlled experimental study may be attributable to replenishment by FFP of the naturally occurring antiprotease system. To investigate this potential therapy further, 202 patients presenting with acute pancreatitis were randomized to receive FFP (2 units daily for 3 days) or a similar volume of colloid control as part of their intravenous fluid therapy. Clinical progress was monitored and the major serum antiproteases (α_1-antiprotease and α_2-macroglobulin) were measured on days 1, 3 and 7. There was no significant difference between the two groups in terms of clinical outcome. α_1-Antiprotease levels rose significantly from day 1 to day 3 in both groups ($P<0\cdot0001$) *and remained elevated at day 7. α_1-Antiprotease is an acute phase protein in man and raised serum levels would be anticipated. FFP appears to have no effect on the magnitude of this rise. Serum α_2-macroglobulin levels were reduced in both groups on day 1 and continued to fall significantly from day 1 to day 3 in the colloid control group* ($P<0\cdot005$) *whilst remaining substantially unaltered in patients receiving FFP* ($P=0\cdot6527$). *α_2-Macroglobulin plays a central role in the elimination of proteases during acute pancreatitis and the ability of relatively low volumes of FFP to reduce the fall in serum α_2-macroglobulin levels seen during the early stages of this disease may have therapeutic implications.*

Keywords: Acute pancreatitis, fresh frozen plasma, serum antiproteases

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Despite improvements in general supportive measures, the mortality from acute pancreatitis in the UK still approaches 10 per cent. Although many specific therapies have been proposed for this disease, none has consistently been shown to improve the outcome in controlled clinical trials.

An uncontrolled clinical study from Dundee[1] reported a low mortality from acute pancreatitis (3·7 per cent) in a consecutive series of patients treated with intravenous fresh frozen plasma (FFP) therapy during the first 5 days of the illness. The total volume of FFP administered ranged from 6 to 11 units (1500–2500 ml). When looking for a mechanism to explain this apparent benefit, the colloid value of FFP was not thought to be significant as it represented only 20–30 per cent of colloid administered to severe cases. A possible explanation was that FFP replenished the levels of naturally occurring antiproteases, particularly α_2-macroglobulin which appears to have a central role in the binding and elimination of the 'toxic broth' of pancreatic enzymes from the tissues and blood stream.

An experimental study performed in Leicester has provided further support for the use of FFP therapy in acute pancreatitis. In an animal model of acute pancreatitis, intravenous infusions incorporating FFP were shown to improve significantly survival at 72 h when compared with animals receiving colloid control ($P<0\cdot01$).

We report the results of a 2-year multicentre controlled clinical trial of low volume FFP therapy in acute pancreatitis.

Patients and methods

This study involved the Leicester General Hospital, the Leicester Royal Infirmary, Glenfield General Hospital, Peterborough District Hospital and the George Eliot Hospital, Nuneaton. During the period from 1 March 1985 to 31 January 1987, patients referred to these surgical units with a clinical diagnosis of acute pancreatitis with serum amylase > 1000 units/l were entered into the trial. One hundred and thirty patients admitted to the Leicester Royal Infirmary during the study period, who were entered into a separate trial of endoscopic sphincterotomy in acute biliary pancreatitis[2], were excluded.

After informed consent the patients were randomized on the opening of a sealed envelope to receive either 2 units of FFP daily for 3 days as part of their intravenous fluid therapy or a similar volume (400 ml daily) of human albumin solution as colloid control. Each hospital used a separate set of randomization envelopes. The remaining intravenous fluid therapy was left entirely to the medical staff looking after the individual patient. An accurate record was kept of all intravenous fluid administered during the first 3 days and any adverse reactions to FFP or human albumin solution were noted.

The nine Glasgow criteria[3] (*Table 1*) for predicting severity in acute pancreatitis were recorded as soon as possible after diagnosis and in any case within 48 h of admission. The presence of three or more of these adverse criteria predicts a severe attack of pancreatitis.

The principal serum antiproteases were measured on days 1, 3 and 7. Serum α_1-antiprotease and α_2-macroglobulin concentrations were

Table 1 *Criteria used to predict severity of attack of acute pancreatitis*[4]

Age	> 55 years
WCC	> 15 × 10^9/l
Urea	> 16 mmol/l
Glucose	> 10 mmol/l
Albumin	< 32 g/l
Calcium	< 2·0 mmol/l
P_aO_2	< 8 kPa
ALT	> 100 units/l
LDH	> 600 units/l

Predicted mild attack: 0–2 factors
Predicted severe attack: 3–9 factors
WCC, white cell count; ALT, alanine aminotransferase; LDH, lactate dehydrogenase

Table 2 *Aetiology of acute pancreatitis*

	Fresh frozen plasma	Colloid control	Total (%)
Gallstones	60	52	56·6
Alcohol	19	22	20·7
Other	6	10	8·1
Idiopathic	14	15	14·6

Table 3 *Distribution of prognostic scores and individual prognostic markers between the treatment groups (median values, range given in parentheses)*

	Fresh frozen plasma	Colloid control	
Predicted severe	34/99	38/99	n.s.*
Prognostic score	2	2	n.s.†
	(0–7)	(0–7)	
Age (years)	59	58	n.s.
	(17–89)	(13–91)	
WCC ($\times 10^9$/l)	14·3	14·3	n.s.
	(5·2–25·0)	(3·3–38·3)	
Urea (mmol/l)	5·5	5·8	n.s.
	(1·5–31·6)	(2·0–61·0)	
Glucose (mmol/l)	7·5	7·55	n.s.
	(4·7–66·4)	(3·6–25·7)	
Albumin (g/l)	37	37	n.s.
	(25–46)	(16–48)	
Calcium (mmol/l)	2·23	2·24	n.s.
	(1·4–2·67)	(1·15–3·09)	
P_aO_2 (kPa)	10·1	10·6	n.s.
	(6·1–17·2)	(5·9–17·8)	
ALT (units/l)	54	59	n.s.
	(4–1111)	(5–846)	
LDH (units/l)	306	351	n.s.
	(71–1800)	(97–3500)	

* χ^2 test
† Wilcoxon rank sum test

measured using goat antisera and Calibrator-1 (Atlantic Antibodies Ltd, Winnersh, Berkshire, UK) on a Cobas Bio centrifugal analyser in turbimetric mode. The subsequent treatment and progress of the patients was carefully recorded on trial pro forma including follow-up of survivors after discharge from hospital. A severe outcome from acute pancreatitis was defined as death, a major complication or a hospital stay exceeding 20 days, having excluded social problems or elective surgery as reasons for prolonging the admission.

The Wilcoxon matched pairs signed ranks test and rank sum test were used to analyse continuous parameters. The χ^2 test was used to analyse clinical variables between the two groups with Yates's corrections where indicated.

Results

Two hundred and three patients were referred for entry into the trial. One patient refused randomized after informed consent and four patients were withdrawn from the trial after randomization. Two of these patients with mild alcoholic pancreatitis were randomized in error as their serum amylase was <1000 units/l. The remaining two patients who had serum amylase levels of <1500 units/l died within 24 h of admission. Post-mortem examination revealed no evidence of acute pancreatitis, death being due to faecal peritonitis in one and multiple pulmonary emboli in the other. This left 198 patients in the study equally randomized to FFP and colloid control groups. The sex distribution was not statistically different with 41 males and 58 females in the FFP group and 54 males and 45 females in the colloid control group. The two groups were well matched in terms of the aetiology of pancreatitis (*Table 2*).

In 78 patients in the FFP group and 83 patients in the colloid control group there had been no previous attack of pancreatitis. The remaining patients (18·6 per cent) had experienced a median of two (range 1–6) previous attacks. Twelve patients were entered into the trial more than once, accounting for a total of 30 attacks of acute pancreatitis. These attacks, which were associated with no mortality, were equally randomized to the two treatment groups.

Thirty-four of the FFP group and 38 of the colloid control group were predicted to be severe on the Glasgow criteria. The distribution of prognostic scores did not differ significantly between the two groups, nor did any of the individual risk factors (*Table 3*). This suggests that the two groups were well matched in terms of predicted severity of pancreatitis.

No statistical difference was demonstrable between the two groups when looking at the level of monitoring which they received or other potential treatments offered for acute pancreatitis (*Table 4*). The only difference between the two groups in terms of treatment was the intravenous fluid therapy. The colloid administered for the purposes of this trial was the only colloid given during the first 3 days in 80·7 per cent of patients. Sixteen patients in the FFP group and 22 patients in the colloid control group received additional colloid during this period. Twenty-six of these patients (68·4 per cent) had predicted severe disease on Glasgow criteria and 17 (44·7 per cent) had severe outcomes. In this group of patients the colloid specified by the trial accounted for a median of 50 per cent (range 10–75 per cent) of colloid administered during the first 3 days.

Three patients developed mild pyrexia and skin rashes whilst receiving FFP. None of these reactions was severe enough to necessitate withdrawing FFP therapy. No other adverse reactions were reported to either FFP or human albumin solution.

There was no statistical difference between the two groups in terms of clinical outcome (*Table 5*). Overall mortality was 8·6 per cent in a total of 17·2 per cent severe outcomes which were evenly distributed amongst the five hospitals involved in the study. The major complications are listed in *Table 6*. To eliminate incidental findings at ultrasound and computerized tomography (CT) scanning, pancreatic mass lesions were only

Table 4 *Comparison of monitoring and other potential treatments offered for acute pancreatitis*

	Fresh frozen plasma	Colloid control	
Monitoring			
Central venous pressure line	14	17	n.s.*
Urinary catheter	49	49	n.s.
Transfer to intensive care unit	5	12	n.s.
Other potential treatments			
Nasogastric tube	56	57	n.s.
Oxygen therapy	36	37	n.s.
Antibiotics	68	61	n.s.
Early surgery	10	9	n.s.
ERCP (+endoscopic sphincterotomy)	6 (3)	7 (3)	n.s.
Calcium infusion	9	3	n.s.
Insulin	5	3	n.s.
Parenteral feeding	7	8	n.s.

* χ^2 test ± Yates's correction

Table 5 *Clinical outcome*

	Fresh frozen plasma	Colloid control	
Severe outcome	14	20	n.s.*
Death	8	9	n.s.*
Median hospital stay (days)	8	9	n.s.†
Range	(3–56)	(3–68)	

* χ^2 test
† Wilcoxon rank sum test

Table 6 *Major complications*

	Fresh frozen plasma	Colloid control
Respiratory complications/failure	8	10
Renal failure	3	4
Cardiac failure	5	4
Multisystem failure	1	6
Pancreatic phlegmon	2	3
Pancreatic pseudocyst	4	6
Pancreatic abscess	2	4
Pancreatic necrosis	0	3
Gastrointestinal haemorrhage	1	4
Gastric outlet obstruction	0	3
Myocardial infarction	1	0
Cerebrovascular accident	0	1
Disseminated intravascular coagulation	1	0
Deep venous thrombosis	1	0
Patients with severe complications	14	20
Deaths	8	9

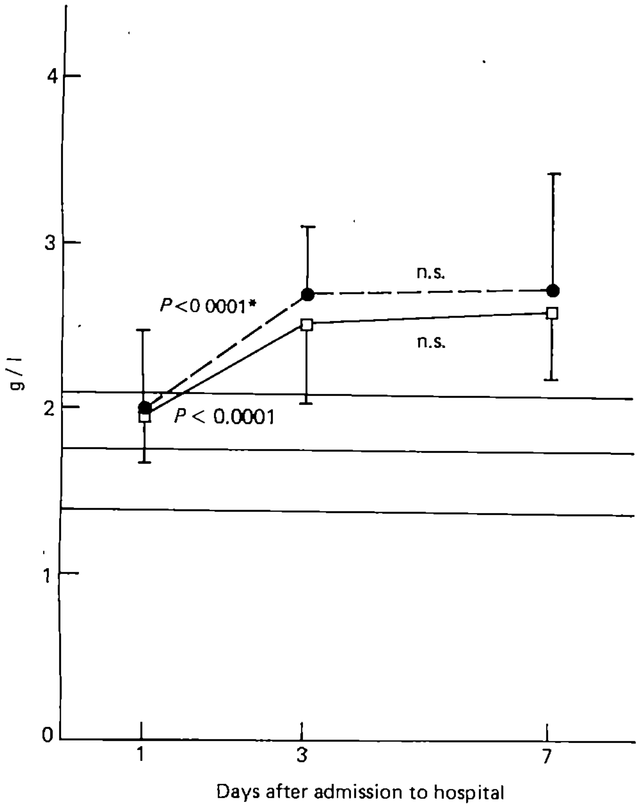

Figure 1 *Serum α_1-antiprotease concentrations in the two treatment groups: □——□, fresh frozen plasma; ●---●, colloid control. The reference range is given as continuous lines. All results are shown as medians with interquartile ranges. *Wilcoxon matched pairs signed rank test*

included as major complications if they resulted in hospital stay in excess of 20 days or if they required percutaneous or surgical drainage. Hospital stay did not differ significantly between the two groups. Patients were followed up for a median of 3·5 months (range 0–22) after discharge from hospital.

Serum α_1-antiprotease levels (*Figure 1*) in both groups were elevated on day 1 when compared to our reference population and a significant rise occurred from day 1 to day 3 ($P<0{\cdot}0001$). Levels remained elevated at day 7. Fresh frozen plasma appeared to have no effect on the magnitude of this rise.

When serum α_2-macroglobulin levels (*Figure 2*) are considered, on all 3 days both groups showed significantly reduced levels compared to our reference population. In the colloid control group α_2-macroglobulin levels fell significantly from day 1 to day 3 ($P<0{\cdot}005$) whilst remaining substantially unaltered in the FFP group ($P=0{\cdot}6527$). The difference between the two groups reached significance on day 3 ($P<0{\cdot}01$). There was no statistically significant change between the levels on day 3 and day 7 in either group.

When the serum antiprotease results are analysed in terms of the severity of clinical outcome, similar changes in α_1-antiprotease levels occurred in mild and severe groups. No statistical differences were present on any day between the mild and severe outcomes within the FFP or colloid control groups.

If the α_2-macroglobulin levels are analysed in the same way, the only difference between the FFP and colloid control groups is that on day 7 levels in the colloid control group were significantly lower in patients with a severe outcome than in patients with a mild outcome ($P<0{\cdot}05$). This difference did not reach significance in the FFP group ($P=0{\cdot}1576$). When both groups are combined, the α_2-macroglobulin levels are significantly lower on day 7 in patients with a severe outcome than in patients with a mild outcome ($P<0{\cdot}01$).

Discussion

Interest in FFP therapy for acute pancreatitis has been stimulated by the publication of an uncontrolled study[1] reporting a low mortality in a consecutive series of 239 patients experiencing 336 separate attacks of acute pancreatitis. The overall mortality was 3·7 per cent per patient population and 2·7 per cent per total number of separate attacks. In an experimental study performed by us in response to this report, intravenous therapy incorporating FFP was shown to improve significantly survival at 72 h in a rat model of acute pancreatitis when compared to colloid control. These two studies appeared to justify a controlled clinical trial of FFP therapy in acute pancreatitis.

When looking for a mechanism to explain the apparent beneficial effect of FFP therapy, the potential colloid value has first to be considered. There is a massive shift from the

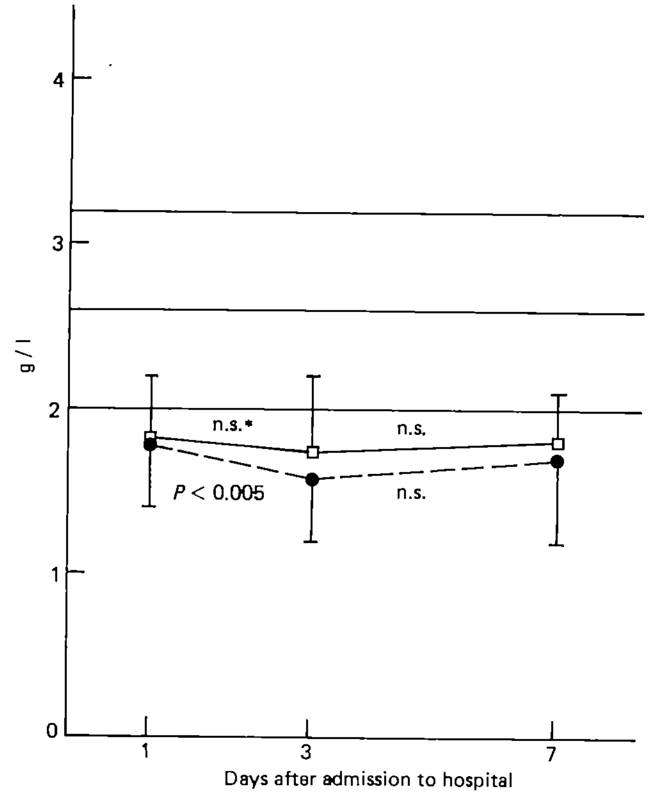

Figure 2 *Serum α_2-macroglobulin concentrations in the two treatment groups: □——□, fresh frozen plasma; ●---●, colloid control. The reference range is given as continuous lines. All results are shown as medians with interquartile ranges. *Wilcoxon matched pairs signed ranks test*

intravascular space in acute pancreatitis and the degree of fluid sequestration correlates with mortality[4,5]. Repletion of the volume deficit improves the clinical outcome, but there is controversy concerning the choice of resuscitative fluid. Both colloid and crystalloid solutions have been shown to be effective in acute pancreatitis[6]. However, because of uncertainty about the value of colloid therapy in acute pancreatitis, a colloid control group was included in the present study. Human albumin solution was useful in this respect as its protein content is almost pure albumin. It is devoid of other potentially valuable proteins present in FFP, and in particular contains no active antiproteases.

Several proteins contained in FFP might be of specific benefit in the therapy of acute pancreatitis. These include clotting factors, fibronectin and C reactive protein; but the replenishment of the plasma antiprotease system is the most promising explanation for the apparent beneficial effect of FFP therapy[1]. The plasma antiproteases constitute by weight the third largest group of functional proteins in human plasma, after albumin and immunoglobulins, accounting for nearly 10 per cent of total plasma protein. They remain active after storage at −20°C in FFP. In man the principal antiproteases are α_1-antiprotease and α_2-macroglobulin which account for more than 90 per cent of antiprotease capacity.

α_1-Antiprotease exhibits an acute phase response with a significant increase in plasma levels during the early stages of acute pancreatitis. The response is displaced slightly, reaching a peak on the fifth or sixth day rather than the third day as seen with other acute phase proteins[7–9]. *In vivo* α_1-antiprotease may only be a temporary inhibitor of trypsin[10] and when complexes of α_1-antiprotease and trypsin are administered intravenously in dog[11] and man[12] the complexes dissociate with the appearance of α_2-macroglobulin–trypsin complexes in blood. α_1-Antiprotease may therefore serve in part as a carrier protein for proteases, particularly in the extracellular space where concentrations of α_2-macroglobulin are low[11–13].

α_2-Macroglobulin may be the final link in the antiprotease chain and its importance is suggested by the fact that complete deficiency of α_2-macroglobulin has not been described in man. It is a very large glycoprotein (725 000 daltons) which forms complexes with a wide variety of proteases. The mechanism of complex formation is unique and involves a rapid conformational change to entrap physically the protease within the bulk of the α_2-macroglobulin[14]. This leaves the active site of the protease still open within the complex to act on smaller molecular weight substrates[15], but the access of larger substrates and inhibitors to the site is sterically hindered. The complexes are very stable and are subsequently rapidly eliminated from the circulation and destroyed by the reticuloendothelial system. The half-life of complexes in the circulation is 10 min in man[12].

During acute pancreatitis plasma levels of α_2-macroglobulin fall as complexing and elimination of α_2-macroglobulin exceeds its production *de novo*. Lowest plasma levels are encountered on day 3, but the more severe the pancreatitis, the more marked and sustained the fall in α_2-macroglobulin levels[8,9,16,17]. Low concentrations of α_2-macroglobulin in plasma and, possibly more importantly, the reflected low concentrations and high saturation of α_2-macroglobulin in peritoneal exudate, may lead to the inappropriate activation by proteases of secondary agents such as the complement and kinin system. These secondary agents may be important mediators of the systemic effects of acute pancreatitis[17].

In the present study FFP was administered during the first 3 days of the illness, the period of time during which plasma α_2-macroglobulin levels are falling most rapidly. Six units were administered which is a similar volume to that used in the Dundee study[1] during this important initial period. The Dundee patients continued to receive FFP to day 5 which may be significant.

Using these relatively small volumes of colloid, no patient had to be withdrawn from the trial because of contra-indications to the fluid therapy such as congestive cardiac failure or acute renal failure. Three possible adverse reactions to FFP were encountered in the form of mild pyrexia and skin rashes. No severe reactions or cases of transmitted infection were recorded. The donors for FFP were screened for antibodies to hepatitis B surface antigen throughout the trial and for antibodies to human immunodeficiency virus from October 1985.

The definition of a severe outcome in acute pancreatitis is difficult. Death is an obviously severe outcome but other criteria which have been used, such as the period of hospital admission, the need for surgery or admission to an intensive care unit, the length of stay in intensive care and the delay before resuming oral intake, are all influenced by the availability of facilities and management policy of individual clinicians. This problem is compounded when several hospitals are involved in the study. We have taken death, the development of a major complication or hospital stay in excess of 20 days as indicating a severe outcome. The use of a shorter period of hospital stay seemed unrealistic in our predominantly elderly population of patients with gallstones. Hospital stays prolonged beyond 20 days purely because of elective surgery or social problems were excluded. Pancreatic mass lesions, demonstrated on ultrasound and CT investigations, were only included as major complications if they resulted in hospital stay in excess of 20 days or if they required surgical or percutaneous drainage.

When including all patients with acute pancreatitis in a controlled trial of a new therapy, over 250 patients are required in each limb to demonstrate a significant reduction in severe outcomes from 20 to 10 per cent with a type one error set at 0·05 and a type two error set at 0·1, and over 550 in each limb to demonstrate a significant reduction in mortality from 10 to 5 per cent[18]. In practice these numbers are difficult to achieve, even with a multicentre study. This problem can be reduced by preselecting a group of patients with more severe disease using methods such as multi-factor analysis[3,4] or diagnostic peritoneal lavage[19]. All patients with acute pancreatitis were entered into this study to reflect the original Dundee work[1]. The decision to terminate the trial was taken after the analysis of 200 patients revealed no significant difference in clinical outcome between the FFP and colloid control groups. The overall incidence of major complications (17·2 per cent) and the mortality (8·6 per cent) reflect the present outcome of acute pancreatitis in this country. It seems likely that, even if low volume FFP does improve clinical outcome, the effect is not significant enough to justify its routine administration to all patients with acute pancreatitis.

α_1-Antiprotease levels showed a significant increase from day 1 to day 3 in both FFP and colloid control groups. Levels remained elevated at day 7. This confirms the acute phase response reported by other workers[7–9]. FFP appears to have no effect on the magnitude of this rise. A delay in the rise of serum α_1-antiprotease levels in severe pancreatitis which has been reported by other workers[9] was not encountered in this study.

The effect of relatively low volumes of FFP on serum α_2-macroglobulin levels was interesting. α_2-Macroglobulin levels were reduced on days 1, 3 and 7 in both the FFP and colloid control groups when compared to the reference population. In the colloid control group α_2-macroglobulin levels continued to fall from day 1 to day 3 ($P<0{\cdot}005$) whilst levels were maintained in the FFP group ($P=0{\cdot}6527$). The difference between the two groups on day 3 was significant with $P<0{\cdot}01$. This conflicts with a recent study[9] in which patients with predicted severe pancreatitis were randomized to receive 3 units of FFP daily or conventional treatment. FFP showed no ability to supplement declining α_2-macroglobulin levels. The numbers of patients involved, however, were small with only three patients receiving FFP and two in the control group. Four of these patients died.

The results of this controlled clinical trial demonstrate that low volume FFP therapy can supplement declining α_2-macroglobulin levels during acute pancreatitis. It is reasonable to speculate that the administration of larger volumes of FFP may result in the normalization of serum α_2-macroglobulin levels. Whether or not this would have any effect on the clinical outcome of acute pancreatitis is unclear. Even though we cannot recommend the use of low volume FFP therapy, a controlled clinical trial of high volume FFP therapy or α_2-macroglobulin concentrates in predicted severe acute pancreatitis seems justifiable.

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Total pancreatectomy for chronic pancreatitis

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A survey of six British centres collected data on 83 patients undergoing total pancreatectomy (TP) for chronic pancreatitis between 1977 and 1986. There were 57 men and 26 women with a median age of 38 years (range 19–61 years). Half were alcoholics and half had had previous acute pancreatitis. Besides jaundice (14 per cent) severe pain was the indication for the operation; regular opiates had been needed in 82 per cent of patients and 37 per cent were addicted to these drugs. All but 12 had had previous pancreatic or biliary surgery, with a median of two operations and a maximum of six. TP was a one-stage procedure in 32 patients, 42 had had distal resections and 9 proximal resections in the past; the pylorus was preserved in 30. Median operation time was 4 h (range 2–18 h) and median blood loss was 3 units (1–21 units). Intraoperative complications in 11 patients included haemorrhage in 9. Four deaths occurred within 30 days from bleeding (2), respiratory failure (1) and Roux-loop infarction (1). All but one of the 79 survivors required full pancreatic supplementation and 38 per cent had difficulties in endocrine control. At a median follow-up of 1·5 years (range 0·25–10 years), 57 patients (72 per cent) were pain-free and 9 (11 per cent) needed only occasional analgesia. Though 13 (17 per cent) still took regular analgesics, all were symptomatically improved. There have been 10 late deaths (13 per cent), all but one of which are attributable to the operation.

Keywords: Total pancreatectomy, chronic pancreatitis

Chronic pancreatitis is an uncommon condition in the UK[1]. It usually presents with abdominal pain and variable degrees of exocrine and endocrine deficiency. Although the deficiency states can be managed by appropriate replacement therapy, the pain is often severe, requiring regular opiate analgesia to which many patients become addicted. Operation is considered for those with crippling pain who may not respond to more conservative treatment such as coeliac plexus blockade. The major aim is to conserve pancreatic function by ductal decompression or partial pancreatic resection. Although initially successful these procedures frequently fail with time, and then nothing short of total pancreatectomy is likely to alleviate the pain. For a small group with end-stage disease, total pancreatectomy may be the initial procedure, particularly if there is already evidence of exocrine and endocrine failure.

In its retroperitoneal position a chronically inflamed pancreas becomes densely bound to the blood vessels and viscera to which it is intimately related. Surgical resection is therefore hazardous. Total pancreatectomy often follows previous operations on the gland and/or nerve blocks, which further complicate the procedure because of the resulting fibrosis. Experience of this operation is largely concentrated in a few referral centres. In November 1985 a workshop was held at the University of Bristol under the auspices of the Pancreatic Society of Great Britain and Ireland to discuss the role of total pancreatectomy in chronic pancreatitis. Some 50 surgeons attended and all those with personal experience of the operation agreed to contribute their cases to this review. At the end of the meeting a proforma was designed and a retrospective survey was undertaken. This paper documents the experience of the contributors over the last 10 years. Although this is clearly not a comprehensive survey of all such operations performed in the UK, most will probably be included.

Patients and methods

Between 1977 and 1986 the six centres reported 83 patients undergoing total pancreatectomy for severe chronic pancreatitis. There were 57 men and 26 women with a median age of 38 years at the time that a total or completion pancreatectomy was performed (range 19–61 years). The distribution of patients by centre is shown in *Table 1*, the largest experience being at the Middlesex Hospital, London. A median of seven total pancreatectomies occurred each year (range 2–16) with an increase in numbers towards the end of the survey (*Figure 1*).

All the contributors were asked to complete a questionnaire detailing the aetiology of chronic pancreatitis, previous treatment and the indication for operation; the degree of pre-operative impairment in pancreatic function was noted. Exocrine function was classified as being normal, impaired if there was a history of steatorrhoea but no replacement therapy, or severe enough to require treatment. Endocrine

Table 1 *Distribution of patients according to the hospital in which the total pancreatectomy was performed*

Bristol Royal Infirmary	12
Manchester Hospitals*	8
Ninewells Hospital, Dundee	11
Glasgow Royal Infirmary	16
Hammersmith Hospital, London	4
Middlesex Hospital, London	32

* Including Manchester Royal Infirmary (5), Withington Hospital (2) and Hope Hospital (1)

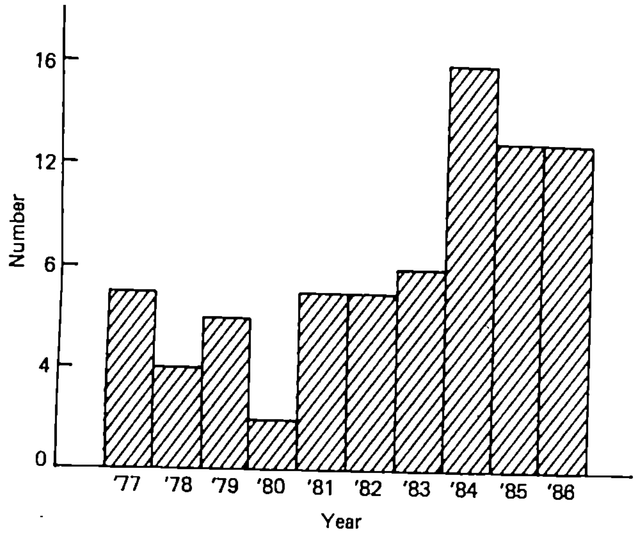

Figure 1 *The number of total pancreatectomies performed each year between 1977 and 1986 in contributing centres*

Table 2 *Aetiology of chronic pancreatitis in 83 patients*

	Male	Female	Total
Alcohol	37	6	43 (52%)
Gallstones	0	4	4 (5%)
Idiopathic	10	8	18 (21%)
Trauma	4	1	5 (6%)
Pancreas divisum	3	7	10 (12%)
Other	1	2	3 (4%)

function was determined as being normal, impaired if there was documented glucose intolerance which might require dietary modification, or requiring injections of insulin. Operative details were sought to include the type of procedure, intra-operative and postoperative complications and blood loss; operative mortality was defined as death in hospital or within 30 days of the procedure. Survival was documented and difficulties with replacement therapy were recorded.

Results

Aetiology (*Table 2*)

Chronic alcoholism was the predominant cause, being present in 43 of the 83 patients (52 per cent), 37 of whom were men. Gallstones were detected in four of the alcoholic patients and were thought to be the main cause of pancreatitis in a further four. Five patients were thought to have developed chronic pancreatitis secondary to trauma, which in three cases was a previous surgical operation; 18 patients were considered to have idiopathic disease. Overall, 43 patients (52 per cent) reported previous multiple acute attacks, which for 10 were thought to be secondary to pancreas divisum. At the time of operation 43 of the patients were regular alcohol drinkers and 50 were smokers.

Presentation

Pain was the overwhelming indication for operation and was severe in all but two patients. Sixty-eight patients (82 per cent) were requiring narcotics to control the pain, and nearly half of these (46 per cent) were thought to be addicted. A previous coeliac plexus block had been tried in 38 per cent.

Most patients were below ideal body weight with a median of 57 kg (range 39–84 kg); 54 reported a weight loss within the previous 3 months (median 8 kg, range 1–30 kg). Vomiting accompanied the pain or the ingestion of analgesics in 32 patients (39 per cent). Twelve patients (15 per cent) had been jaundiced at some time during their illness. The differences between patients with alcoholic chronic pancreatitis and the other patients are shown in *Table 3*.

Investigation

Specific details of imaging studies were not recorded as part of this view but 40 per cent of patients had pancreatic calcification. The most useful investigation was a ductogram obtained endoscopically (88 per cent) or operatively (9 per cent), and this was available in all but two patients. A pre-operative angiogram was performed in nine patients (11 per cent). Fifty-one patients had evidence of exocrine pancreatic failure, but only 19 were requiring insulin (*Table 4*). Indeed 60 per cent of patients had no evidence of glucose intolerance before total pancreatectomy. There was no appreciable difference between those with alcohol- and non-alcohol-related pancreatitis.

Operation

Seventy-one of the 83 patients (86 per cent) had undergone a previous pancreatobiliary procedure on one or more occasions (median 2, range 0–6 operations). In addition, 14 patients had had other abdominal operations. Forty-two patients (51 per cent) gave a history of a previous distal pancreatectomy at a median of 1·5 years previously (range 0·25–8 years), whilst only nine had had a previous proximal resection (11 per cent). For 32 patients (38 per cent), total pancreatectomy was the primary resection. Although 27 patients had had previous drainage operations performed to deal with cysts or combined with partial resections, only four had had a pancreaticojejunostomy as a single procedure.

Fifty-three patients (64 per cent) underwent a conventional total pancreatic resection with a hemigastrectomy and gastrojejunostomy. In an attempt to reduce the postoperative morbidity, the pylorus and duodenal cap were preserved in 10 patients and the pylorus and entire duodenum were preserved in 20 patients (at the Middlesex Hospital). Thus gastric resection was avoided in 30 of the 83 patients (36 per cent). The various forms of total pancreatectomy took a median of 4 h to complete (range 2–18) and used a median of 3 units of blood (range 1–21 units).

Major intra-operative complications occurred in 11 patients (13 per cent), notably severe bleeding in 9 patients. In two cases with portal hypertension, damage to the portal vein led to severe haemorrhage and ultimately death. Four of the other seven patients also bled from a portal vein injury, whilst one was bleeding from the splenic vein. The remaining cases were due to

Table 3 *Presenting features in 83 patients with chronic pancreatitis divided by aetiology*

	Alcoholic	Other
Sex	37M:6F	20M:20F
Requiring opiates	39 (91%)	29 (72%)
Vomiting	20 (46%)	12 (30%)
Jaundice	9 (21%)	3 (7·5%)
Median pre-operative weight	55 kg	58 kg
Calcification	27 (63%)	6 (15%)

Table 4 *Pancreatic function in 83 patients before total pancreatectomy*

	Exocrine function		Endocrine function	
	No.	%	No.	%
Normal function	32	39	51	61
Impaired function	26	31	13	16
On replacement therapy	25	30	19	23

Table 5 *Postoperative complications experienced in 36 patients of the 83 patients undergoing total pancreatectomy*

Haemorrhage	
Intraperitoneal	2
Gastrointestinal	2
Enteric leak	4
Biliary obstruction	2
Sepsis	
Wound	6
Chest	13
Urinary	3
Abdominal	7
Pneumothorax	2
Deep vein thrombosis	2
Air embolus	1

Table 6 *Causes and timing of 10 late deaths following total pancreatectomy for chronic pancreatitis*

Cause	Time after operation (months)
Myocardial infarct*	3
Pancreatic cancer*	3
Abdominal sepsis*	3
Hypoglycaemia*	3
Abdominal sepsis	6
Hyperglycaemia*	15
Hypoglycaemia, ? suicide*	30
Addict, narcotic overdose	48
Alcoholic-related traffic accident*	60
Alcohol-related fall*	66

* Patient with alcohol-related chronic pancreatitis

a splenic capsular tear and accidental division of the superior mesenteric artery, respectively. Colonic resection and a colostomy were required in two patients who developed ischaemic damages following dissection of an adherent transverse mesocolon.

Outcome

Four patients (three alcoholic) died in the postoperative period giving a mortality rate of 4·8 per cent. Two of the deaths resulted from continuing haemorrhage and a third from respiratory failure. The fourth death was due to infarction of a pre-existing Roux loop which was damaged at a completion pancreatectomy. Of the 79 survivors, 36 (46 per cent) suffered one or more postoperative complications mostly as a result of pulmonary or intra-abdominal sepsis (*Table 5*), with no difference between alcoholics and non-alcoholics. The avoidance of a pancreatic anastomosis resulted in only four enteric leaks (biliary 2, duodenal 2), none of which was fatal.

The follow-up period ranges from 3 months to 10 years. In view of the increasing number of operations performed in the last 3 years, the median review time is only 18 months. During this time there have been 10 further deaths (13 per cent) of which several were directly related to the chronic pancreatitis and subsequent pancreatectomy (*Table 6*). Four of the deaths probably stemmed from difficulty with insulin control. One patient died 3 months postoperatively from carcinomatosis. The total pancreatectomy was performed for a gland completely affected by chronic pancreatitis and a small carcinoma was discovered only on histological examination; following surgery tumour progression was rapid. Other late complications included four patients with small bowel obstruction, three with late intra-abdominal sepsis and four cases of peptic ulceration.

All but two patients required full pancreatic supplementation. One patient had a tiny rim of uncinate process left on the portal vein which functioned sufficiently well at first to avoid the need for insulin. Diabetic control is frequently a problem in this group of unreliable patients: 30 patients, of whom 19 were alcoholic (38 per cent), had difficulties requiring hospital admission due to hypoglycaemia. Poor control with enzyme supplementation was recorded in 21 patients (14 alcoholic, 27 per cent). One patient, however, altered his diet and tolerated the steatorrhoea rather than take a large number of tablets.

The prime aim of operation was pain relief, and this was complete in 57 patients (72 per cent) who required no further analgesia. Nine patients required only non-opiate medication once or twice a week, so that overall 84 per cent were greatly improved. The remaining 13 patients continued to require regular analgesia although of a reduced dose or potency; six patients still require occasional narcotics. The operation appeared to be equally effective in alcoholic and non-alcoholic patients (*Table 7*).

Discussion

Whatever the cause of chronic pancreatitis, the outstanding indication for resection of the whole or residual pancreas was pain, which was usually severe and disabling. Over 80 per cent of patients required narcotic analgesia, often in substantial doses, despite previous coeliac plexus blockade in 38 per cent. This need for long-term and powerful analgesia, coupled in some cases with personality upset, underlies the high addiction rate of 37 per cent.

Total pancreatectomy is an uncommon operation for chronic pancreatitis and is usually undertaken as a last resort when more conservative measures have failed to relieve the symptoms. In his 1978 review of the world literature, Braasch *et al.*[2] could only collect 53 cases. The only other big series is that of Gall *et al.*[3] who reported 68 total resections in 1981. Seventy-one of our patients (86 per cent) had had at least one operative procedure for their pancreatitis, in fifty-one cases a partial resection. It is worth noting that 42 patients came to further resection within 18 months of distal pancreatectomy. Although distal resection is easier than proximal resection, it may be less effective treatment for most patients with chronic pancreatitis[2–5]. Indeed distal resection of 40–80 per cent of the gland has been shown to have the highest morbidity while at the same time achieving the least in terms of pain relief[4]. These data fit with Longmire's contention[6] that the head of the pancreas is the pacemaker of chronic pancreatitis. If partial resection is indicated, a proximal resection can be performed with low mortality and prolonged survival[4,5,7,8]. Although total pancreatectomy is reserved for end-stage pancreatitis, it is rather surprising to find that about 40 per cent of our patients had near-normal pancreatic function. Indeed, despite the frequency of previous partial resection, 60 per cent had no evidence of glucose intolerance; these findings are similar to the German series where only 42 per cent of patients had diabetes mellitus before total pancreatectomy[3]. In these cases, the pain was so severe that the resultant deficiency states were accepted as the price of effective analgesia.

Total pancreatectomy is generally effective in relieving pain. Only 16 per cent of our patients needed analgesics on a daily basis afterwards, and most of these reported an improvement in the severity of pain; only three addicts remained on regular narcotics. Nevertheless, total pancreatectomy is a major undertaking and clearly not without risk. Our mortality rate of 4·8 per cent seems acceptable for such an extensive procedure, especially when it is often a third or fourth surgical attack on the

Table 7 *Analgesic requirement in 79 survivors of total pancreatectomy*

	Alcoholic ($n=40$)	Other ($n=39$)
No analgesia	30	27
Occasional analgesia	5	4
Regular analgesia	5	8

pancreas. Both Braasch *et al.*[2] and Kiviluoto *et al.*[9] have reported small series without operative mortality, but our figure is similar to that published for proximal pancreaticoduodenectomy[3,5] and considerably less than the 20·6 per cent reported by Gall[3]. Subtotal (85–95 per cent) distal resection seems an unattractive alternative as diabetes is almost inevitable, morbidity and mortality are not avoided, with bile duct injury and duodenal devascularization as specific complications; moreover, pain relief is unreliable[10,11]. Indeed even the original protagonists of this operation are moving to proximal resection as a superior procedure[11].

Our results underline the importance of referring these patients to specialist centres, and the small number of patients requiring total pancreatectomy in Britain at present makes such referral feasible. Postoperative complications are common and good intensive care facilities are required. The most serious problem is haemorrhage, which was responsible for two deaths and four major complications. The patients are often malnourished and sepsis is also common. The lack of a pancreatic anastomosis removes one major possible complication and only four patients had an enteric leak, none of which was fatal.

The median follow-up here is short (18 months), but even within this period there is a disturbing incidence of late deaths (13 per cent). Figures of 10–40 per cent have been reported for deaths within 5 years of resection for chronic pancreatitis and the risk is especially high in those who continue to drink[2,9,11–13]. Indeed, 8 of the 10 late deaths in our series were of alcoholics, although they comprised only half the total group. Problems with diabetic control are common and in four cases led to death; other authors[2,3,9] report both this problem and the frequent readmission rate of their patients in hypoglycaemic states. Gall[3] described a late mortality rate of 19 per cent with half of the deaths attributable to hypoglycaemia. The inevitable diabetes following total pancreatectomy is aggravated by an incontinent gastric remnant resulting from the classical operation. Such diabetes is difficult to control as rapid gastric emptying leads to peaks and troughs in the serum glucose, which are difficult to avoid with insulin administered once or twice daily; an added problem may be the loss of glucagon secondary to the duodenectomy[14]. Two alternative approaches to this are pylorus preservation as described by Traverso and Longmire[15] and duodenal preservation described by Russell[16]. Early results are encouraging and preservation of an intact stomach is possible with a low morbidity and improved diabetic control[15,17,18]; preservation of the entire duodenum must still be considered experimental but has the theoretical advantage of maintaining glucagon production[16]. Although attractive, technical problems may render such conservative procedures impossible, and their theoretical superiority should certainly not be allowed to jeopardize the patient. Ten of the duodenum-preserving resections were performed for chronic pancreatitis in association with pancreas divisum, which is generally an uncommon indication for resection[19].

Total pancreatectomy will continue to be justified by its ability to control pain that is resistant to any other lesser procedure. The initial operative morbidity and mortality rates are probably acceptable, but the late mortality rate is a continuing source of concern and life-time surveillance of these patients is required.

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Study of common bile duct exploration and endoscopic sphincterotomy in a consecutive series of 438 patients

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The outcome of 438 consecutive patients who had exploration of the common bile duct and/or endoscopic sphincterotomy (ES) in a 5-year period was reviewed. Patients were analysed according to four groups: 59 patients had planned ES followed by surgery resulting in 14 major complications (23·7 per cent) including 3 deaths (5·1 per cent) (group 1); 248 patients had surgery alone with 21 major complications (8·5 per cent) including 10 deaths (4·0 per cent) (group 2); 114 patients with gallbladder in situ *underwent ES alone with 22 major complications (19·3 per cent) including 9 deaths (7·9 per cent) (group 3); 17 patients with remote cholecystectomy also had ES alone with 3 major complications (17·6 per cent) including 3 deaths (17·6 per cent) (group 4). There was no difference in mortality between the groups. Compared with group 2, major complications were significantly higher in group 1 ($\chi^2 = 11{\cdot}0$, d.f. = 1, P < 0·001) and in group 3 ($\chi^2 = 8{\cdot}6$, d.f. = 1, P < 0·003). Patients in group 3, however, were significantly older than those in groups 1 and 2, and the former also had higher medical and total risk factor scores than the latter (all P < 0·001). The results indicate that routine pre-operative ES is of questionable value. ES alone is justified in elderly high risk patients; mortality in this group might be reduced by improved management of post-ES complications.*

Keywords: Choledocholithiasis, endoscopic retrograde cholangiopancreatography, endoscopic sphincterotomy

The complication rate following surgery for common bile duct (CBD) stones is up to 46 per cent[1] with a CBD clearance rate of 89–97 per cent[2–6] and a mortality rate which varies from 2 to 8 per cent[1–9]. The clearance rate of CBD stones by endoscopic sphincterotomy (ES) is similar but a lower complication rate of 10–15 per cent and a lower mortality rate of less than 3 per cent is often reported[10,11]. These figures suggest that ES is superior to surgery in the treatment of CBD stones. Additional advantages of ES are that it is quicker to perform than surgery, requires only a brief period of hospitalization and is therefore more acceptable to patients.

A major drawback of ES is that it does not deal with existing or subsequent complications due to remaining gallbladder stones[10–12]. Assuming the validity of these figures it follows that ES should be preferred in three situations. First, when there are retained or recurrent CBD stones after cholecystectomy; secondly, as a deliberate manoeuvre before surgery (i.e. cholecystectomy); thirdly, in 'high operative risk' patients in whom the potential risks of surgery outweigh the risk of developing post-ES complications.

This line of reasoning has not been properly validated by clinical results because of two main problems. First, series of patients have been reported as undergoing either surgery or ES; the patients in these series are usually preselected either because of personal or institutional bias and/or because of differing referral patterns. Secondly, there has been a uniform lack of use of 'risk factors' to define the populations studied.

The aim of the present study was to review the outcome of all patients presenting to a single centre from a defined population, irrespective of the treatment received (namely, surgery, ES or a combination of these) with the use of previously reported 'risk factors'[3–16] to describe each of the treatment groups.

Methods

The case notes of all patients undergoing surgical choledochotomy and/or ES for CBD stones during a 5-year period (1981–1985) presenting to the two main Leicester hospitals (catchment population of 850 000) were reviewed. Patients were identified first, by the use of the Hospital Activity Analysis diagnostic and operation codes, secondly, by reference to the prospectively recorded data base of patients who had undergone endoscopic retrograde cholangiopancreatographic (ERCP) examination and thirdly, by the use of the diagnostic and operation codes entered into a prospective surgical audit in one of the two hospitals.

Patients were divided into four groups: those who were intended and agreed to undergo ES followed by surgery as a deliberate manoeuvre (group 1); those who underwent surgery without previous ES (group 2); those who underwent ES as the only intended procedure either with gallbladder *in situ* (group 3) or after remote cholecystectomy (group 4).

Clinical, biochemical, haematological and medical risk factors[13–16] (*Table 1*) were recorded. ERCP and ES were performed using standard techniques involving an active CBD stone extraction policy as previously described[12]. Patients who were referred from outside the

Table 1 *Risk factors used to compare different treatment groups*

Major	Minor	Medical
Bilirubin > 200 µmol/l	Bilirubin 100–200 µmol/l	Hypertension
Haematocrit < 30%	Alkaline phosphatase > 260 units/l	Heart disease
White cell count > 10 × 10⁹/l	Alanine transaminase > 100 units/l	Chronic lung disease
Creatinine > 130 µmol/l	Temperature > 38°C	Steroid Rx
Albumin < 30 g/l	Age > 60 years	
	Diabetes mellitus	

Table 2 *Distribution of sex and major clinical presentation between the four groups*

	Group				χ^2 test		
	1 ($n=59$)	2 ($n=248$)	3 ($n=114$)	4 ($n=17$)	χ^2	d.f.	P
Women	32 (54)	158 (64)	71 (62)	12 (71)	1·7	3	n.s.
Jaundice present	34 (58)	90 (36)	91 (80)	10 (59)	74·9	6	0·0001
History of jaundice	13 (22)	48 (19)	0	0			
Temperature >38°C	10 (17)	27 (11)	31 (27)	2 (12)	20·3	6	0·0025
History of temperature >38°C	3 (5)	6 (2)	0	0			
Acute cholangitis	7 (12)	18 (7)	20 (18)	1 (6)	10·7	6	0·0963
History of cholangitis	3 (5)	0	0	0			
Acute pancreatitis	3 (5)	10 (4)	18 (16)	1 (6)	30·5	6	0·0001
History of pancreatitis	1 (2)	22 (9)	0	0			

Numbers in parentheses are percentages

Table 3 *Comparison of age, haematological and biochemical variables and risk factor scores between the four groups*

Function	Group 1	2	3	4	Analysis of variance P	Contrasts†
Age (years)	60·0 (20–83)	57·9 (18–89)	75·7 (33–92)	64·1 (22–88)	$<0·0001$	b and d(***), f(*)
Haemoglobin (g/dl)	13·8 (10·0–16·7)	13·7 (9·1–17·5)	13·1 (4·4–16·8)	13·8 (11·1–16·0)	0·0157	b(*), d(**)
Haematocrit (%)	40·7 (28·8–49·3)	41·0 (30·5–51·5)	39·4 (22·5–50·6)	42·1 (34·4–49·1)	0·0364	d and f(*)
White cell count ($\times 10^9$/l)	9·0 (2·5–21·8)	8·4 (3·2–21·8)	10·8 (1·2–40·6)	9·5 (4·9–19·6)	0·0001	b(*), d(***)
Urea (mmol/l)	5·4 (1·9–19)	5·1 (1·9–25·7)	7·5 (2·1–28·7)	4·6 (2·0–9·5)	$<0·0001$	b(**), d(***), f(*)
Creatinine (μmol/l)	93 (45–280)	88 (4–377)	100 (10–304)	80 (44–157)	0·0464	d(*), b($^{+++}$)
Total protein (g/l)	67 (51–82)	67 (20–85)	64 (40–82)	67 (58–77)	0·0231	b(**), d(**)
Albumin (g/l)	38 (26–48)	39 (22–72)	35 (24–46)	38 (30–44)	$<0·0001$	a(*), b(**), d(***)
Alkaline phosphatase (units/l)	453 (62–2629)	311 (20–1548)	544 (85–3074)	391 (76–886)	$<0·0001$	a(*), d(***)
γ-Glutamyl transpeptidase (units/l)	354 (11–1914)	258 (5–1891)	383 (10–1926)	396 (10–972)	0·0065	d(***)
Alanine transaminase (units/l)	216 (4–1134)	141 (1–902)	160 (10–612)	134 (20–359)	0·0608	a(*), d($^{+++}$)
Bilirubin (μmol/l)	110 (3–550)	76 (3–841)	98 (5–709)	91 (9–683)	n.s	d($^{+++}$)
Medical risk factors	0·41 (0–2)	0·32 (0–3)	2·57 (0–5)	2·29 (0–5)	$<0·0001$	b, c, d and e(***)
Total risk factors	2·9 (0–8)	2·0 (0–8)	3·6 (1–7)	2·8 (0–6)	$<0·0001$	a(***), b and d(**)

Values are means with ranges in parentheses.
† Contrasts of groups: a = 1 *versus* 2; b = 1 *versus* 3; c = 1 *versus* 4; d = 2 *versus* 3; e = 2 *versus* 4; f = 3 *versus* 4; * = $P<0·05$; ** = $P<0·01$; *** = $P<0·001$ by Duncan's multiple range testing; $^{+++}$ = $P<0·001$, by Mann–Whitney *U* test

Leicester area to one of the well known ERCP specialists were excluded from the analysis in order to reduce bias. Success or failure to extract fully all CBD stones was recorded along with any ensuing complications. With respect to surgery, the type of operation, the grade of surgeon who undertook the operation, the use of peroperative cholangiography (POC) and the findings at operation were also recorded. For all groups, outcome was qualified by minor (non-life threatening) complications and major (life threatening) complications.

Statistical analysis

All the information was coded and entered into a mainframe computer for analysis using the BMDP (University of California, USA) and Minitab (Pennsylvania State University, USA) statistical programs. Discrete variables were analysed by the χ^2 test. Continuous variables were tested using analysis variance (ANOVA). Where significant differences were detected using ANOVA, suitable linear contrasts were employed using Duncan's correction, for four means, for all significance levels ($P=0·05$ taken as minimum significance level). The Mann–Whitney *U* test was also used in selected cases.

Results

Presenting features of groups 1–4

A total of 438 patients were identified with a mean age of 62·9 years (range 18–92 years). The numbers in each group with their presenting clinical, haematological and biochemical variables are shown in *Tables 2* and *3*. Jaundice, fever >38°C, acute cholangitis and acute pancreatitis were more common in patients in group 3 (ES only) compared with the other groups (*Table 2*). Compared with the two surgical groups (1 and 2) patients in group 3 were older, had a higher mean blood white cell count and had increased serum levels of urea, creatinine, liver enzyme and bilirubin; the latter patients also had a lower mean blood haemoglobin and haematocrit and a lower serum level of albumin (*Table 3*). Medical risk factor scores were also greater in the two ES only groups (3 and 4) compared with the

Table 4 *Details of immediate complications according to groups following attempted endoscopic sphincterotomy and stone extraction*

	Group				
Complication	1 (n=59)	3 (n=114)	4 (n=17)	Total (n=190)	Percentage
Acute cholangitis	5 (2*)	9 (5*)	1	15	7·9
Post-ES bleeding	1	3	1	5	2·6
Septicaemia	0	3 (1*)	1	4	2·1
Acute pancreatitis	2	1	0	3	1·6
Empyema of gallbladder	0	2 (2*)	0	2	1·1
Gastric erosions	0	2 (2*)	0	2	1·1
Cardiac failure	0	2	0	2	1·1
Variceal bleeding	0	0	1	1	0·5
Perforation	1	0	0	1	0·5
Minor complications	2	2	1‡	5	2·6
Major complications	6	19	3	28	14·7
Deaths	1 (2†)	8 (1†)	2 (1†)	11 (4†)	5·8 (2·1†)

* Number with pre-existing acute cholangitis; † additional deaths following surgery; ‡ occurred in a patient who had a major complication

Table 5 *Relationship of complications to failed stone extraction in 190 patients undergoing endoscopic sphincterotomy*

		Endoscopic stone extraction					
		Successful n=156 (82) Complications			Failed n=34 (18) Complications		
Group	n	None	Minor	Major	None	Minor	Major
1	59	42	1	2	9	1	4
3	114	85	1	13	8	1	6
4	17	10	0	2	4	0	1
Total	190	137 (87·8)	2 (1·3)	17 (10·9)	21 (61·8)	2 (5·9)	11 (32·3)

Numbers in parentheses are percentages

Table 6 *Operative details in 325 patients according to groups*

		Cholecystectomy plus				
Group	n	SDE	TDS	CDD	SDE/TDS	Cholecystectomy only
1	58	14	1	3	3	37
2	248	171	15	46	16	0
3	14	6	1	1	4	2
4	5	0	1	1	3	0
Total	325	191 (58·8)	18 (5·5)	51 (15·7)	26 (8·0)	39 (12·0)

Numbers in parentheses are percentages.
SDE, supraduodenal exploration; TDS, transduodenal exploration; CDD, choledochoduodenostomy

Table 7 *Details of postoperative complications in 325 patients according to group*

	Group				
Complications	1 (n=58)	2 (n=248)	3 (n=14)	4 (n=5)	Total (n=325)
Wound infection	9	26 (1*)	3	2	40 (12·3%)
Respiratory failure	5	15	5	0	25 (7·7%)
Biliary leak	2	17 (5*)	1	0	20 (6·2%)
Haemorrhage	2	7 (1*)	0	1	10 (3·1%)
Intra-abdominal abscess	1	9 (2*)	0	0	10 (3·1%)
T tube complications*	0	5	0	0	5 (2·2%)†
Septicaemia	1	5	0	0	6 (1·8%)
Bacteraemia	2	4	0	0	6 (1·8%)
Renal failure	1	3	0	0	4 (1·2%)
Pulmonary embolus	0	3	0	0	3 (0·9%)
Acute pancreatitis	0	2	1	0	3 (0·9%)
Cerebrovascular accident	0	2	0	0	2 (0·6%)
Minor complications	12	35	3	1	51 (15·7%)
Major complications	8	21	3	1	33 (10·2%)
Deaths	2	10	1	1	14 (4·3%)

* Complications directly attributable to early T tube dislodgement or removal. † 223 T tubes were inserted

planned surgery groups (1 and 2) (*Table 3*). These factors combined to give the main ES only group a greater total risk factor score compared with the two surgical groups (*Table 3*).

Endoscopic CBD stone extraction

This was attempted in 190 patients, comprising patients in groups 1, 3 and 4, by 4 different endoscopists. All these patients had CBD stones confirmed. Endoscopic sphincterotomy and complete stone extraction was successful in 156 cases. Post-ES complications occurred in 32 patients (16·8 per cent) with 11 deaths (5·8 per cent) (*Table 4*). A total of 77 patients went on to have surgery: this was as planned in 58 patients in group 1 and in 19 cases from groups 3 and 4 because of complications and/or failure to extract stones. There were an additional four deaths following surgery, giving an overall mortality associated with ES of 7·9 per cent. Overall, complications were significantly more common in cases where ES either failed or stone extraction was incomplete (χ^2=14·44, d.f.=1, P<0·001) (*Table 5*). Inexperienced endoscopists had more complications, but this difference was not statistically significant.

Surgery. This was undertaken in a total of 325 patients *Table 6*). Exploration of the CBD was undertaken in 286 patients with CBD stones confirmed in 238 cases (83·2 per cent). Consultants performed 192 operations (59 per cent), 89 operations were performed by senior registrars (27 per cent) and 44 operations were undertaken by registrars (14 per cent). Peroperative cholangiography (POC) was performed in 242 cases (74 per cent); in 51 cases postexploratory cholangiograms were also performed (16 per cent). Consultant staff undertook POC in 131 cases (68 per cent), senior registrars performed POC in 69 cases (78 per cent) and registrars performed POC in 42 cases (96 per cent) (χ^2=19·04, d.f.=2, P<0·001).

There were 84 patients with complications (25·9 per cent) including 4 deaths (4·3 per cent) (*Table 7*). In 223 operations 'T' tubes (all latex) were inserted with major complications occurring in 5 cases owing to early T tube dislodgement or removal (at 3–8 days). In all five cases 3/0 or 4/0 catgut was used to close the choledochotomy around the T tube limbs; guttering of the T tube limbs with excision of a 'V' at the T junction was not used in these cases.

Twenty-six patients were found to have retained stones, representing 9·1 per cent of all explorations or 10·9 per cent of cases of confirmed CBD stones. The incidence of retained stones was not related to the use of POC, the type of operation or to the presence of multiple or single CBD stones. These 26 cases were managed by ES and stone extraction in 22 cases (no complications) by normal-saline flushing in 1 case and dissolution by mono-octanoin infusion in another case. The remaining two patients died from complications in the postoperative period.

No significant relationship was found between the grade of surgeon, the number of CBD stones, the type of operation performed, the finding of retained stones or the development of postoperative complications.

Table 8 *Overall outcome between the four groups*

	Group			
Complications	1 ($n=59$)	2 ($n=248$)	3 ($n=114$)	4 ($n=17$)
Minor	14 (23·7)	35 (14·1)	6 (5·3)	1 (5·9)
Major	14 (23·7)	21 (8·5)	22 (19·3)	3 (17·6)
Deaths	3 (5·1)	10 (4·0)	9 (7·9)	3 (17·6)

Numbers in parentheses are percentages

Overall outcome. There was no significant difference between any of the groups in terms of mortality (*Table 8*). There was however a higher incidence of major complications in patients in group 1 (pre-operative ES) compared with group 2 (surgery only) ($\chi^2 = 11{\cdot}0$, d.f. = 1, $P < 0{\cdot}001$), and a higher incidence of major complications in group 3 compared with group 2 ($\chi^2 = 8{\cdot}75$, d.f. = 1, $P = 0{\cdot}003$). Overall, 25 patients died in the whole series (5·7 per cent); precise details are shown in *Table 9*.

Table 9 *Cause of death in the 25 cases occurring in the total series of 438 patients*

Patient	Sex	Age (years)	MRF (n)	TRF (n)	Presentation procedure (see footnote)	Cause of death
Group 1						
1	F	64	0	3	Complete stone extraction, inadvertent choledochotomy	Bronchopneumonia (day 20)
2	M	72	1	3	Failed stone extraction, retroperitoneal perforation, emergency supraduodenal exploration	Bronchopneumonia (day 5)
3	M	63	0	4	Failed stone extraction, awaiting surgery	Acute cholangitis (day 8)
Group 2						
4	F	74	0	3	Choledochoduodenostomy	Pulmonary embolus (day 21)
5	M	71	1	2	Choledochoduodenostomy	Myocardial infarct (day 30)
6	F	71	1	2	Choledochoduodenostomy	Acute pancreatitis, cardiorespiratory failure (day 20)
7	M	71	1	6	Acute cholangitis, supraduodenal exploration, retained stone	Renal failure, respiratory failure (day 1)
8	M	83	1	3	Large stone eroding common bile duct, hepaticojejunostomy	Cardiorespiratory failure (day 4)
9	M	68	1	3	Choledochoduodenostomy	Septicaemia, renal failure, respiratory failure (day 18)
10	F	44	0	0	Choledochoduodenostomy, retained stone	Bile leak, septicaemia (day 25)
11	F	44	1	4	Nelson's syndrome, transduodenal sphincterotomy	Acute pancreatitis, multisystem failure (day 30)
12	F	75	2	4	Acute cholangitis with pancreatitis and perforated gallbladder, supraduodenal exploration	Pulmonary embolus, respiratory failure (day 1)
13	F	75	1	7	Large stone eroding through common bile duct, hepaticojejunostomy	Bile leak, acute cholangitis, renal failure (day 31)
Group 3						
14	M	68	3	5	Complete stone extraction, no surgery	Cardiac failure (day 20)
15	M	89	3	5	Acute cholangitis, complete stone extraction, no surgery	Empyema of gallbladder, acute cholangitis (day 5)
16	F	74	2	3	Acute cholangitis, complete stone extraction, no surgery	Acute cholangitis (day 3)
17	F	74	3	4	Impacted stone, needle choledochoduodenostomy, emergency supraduodenal exploration	Acute pancreatitis, respiratory failure (day 5)
18	F	81	3	4	Acute cholangitis, complete stone extraction, no surgery	Gastric erosions (day 21)
19	F	85	3	4	Failed stone extraction, nasobiliary catheter, no surgery	Atrial fibrillation (day 5)
20	F	71	3	4	Acute cholangitis, incomplete stone extraction, no surgery	Respiratory failure, acute cholangitis (day 8)
21	M	84	1	5	Failed initial stone extraction, no surgery	Acute cholangitis (day 10)
22	M	76	3	4	Incomplete stone clearance, no surgery	Septicaemia (day 31)
Group 4						
23	M	72	3	4	Complete stone clearance, no surgery	Variceal bleeding, pancreatic cancer (day 20)
24	M	63	2	4	Incomplete stone clearance, no surgery	Septicaemia (day 16)
25	M	79	2	3	Acute pancreatitis, failed sphincterotomy, supraduodenal and transduodenal exploration	Acute cholangitis, septicaemia (day 26)

All patients presented with jaundice and had common bile duct stones and all patients in groups 1–3 had cholecystectomy during surgery. MRF, medical risk factors; TRF, total risk factors

Table 10 *Relationship of death to age, the medical risk factor score and the total risk factor score*

	Deaths/total	Percentage
Age band (years)		
18–59	2/154	1·3
60–69	5/106	4·7
70–92	18/178	10·1
Medical risk factors (*n*)		
0	4/232	1·7
1–2	13/129	10·1
3–5	8/70	11·4
Total risk factors (*n*)		
0–1	1/40	0·3
2–3	9/162	5·5
4–8	15/136	11·0

Deaths were shown to be significantly related to age, the medical risk factor score, and the total risk factor score (all $P<0{\cdot}001$) (*Table 10*).

Discussion

The overall mortality in the present series was 5·7 per cent and is similar to series of surgical CBD exploration with figures of 6·5 per cent reported by Doyle *et al.*[7] and of 7·4 per cent reported by Vellacott and Powell[6]. Other large surgical series have indicated mortality rates ranging from 2·1 to 4·3 per cent[1–5,8,9]. Thompson has recently reported 2 deaths out of a group of 113 patients (1·8 per cent) in whom either surgery or ES was performed depending on clinical grounds[17].

Despite the introduction of 'risk' factors to describe patients undergoing biliary tract surgery[13–16], there are no series before this which provide sufficient detail to permit strict comparisons. Nevertheless some general comments are possible. In each of the studies of surgical CBD exploration referred to above the proportion of patients who were actually found to have CBD stones ranged from 51 to 73 per cent[1–7,9]. Yet it is clearly established that the presence of CBD stones substantially increases the postoperative mortality[4,6,7,18]. In the present series 89·3 per cent of the patients had CBD stones. In a recently published series from Rotterdam the mortality rate of surgical CBD exploration in 1007 patients was impressively low (2·1 per cent)[9]. In the Dutch series, however, only 557 patients (55 per cent) actually had CBD stones which is much lower than that in the present series ($\chi^2=249$, d.f.$=1$, $P<0{\cdot}0001$). Similarly, the Dutch series had a lower proportion of patients aged over 70 years (35 *versus* 41 per cent; $\chi^2=4{\cdot}6$, d.f.$=1$, $P=0{\cdot}0332$) and patients aged over 80 years (8 *versus* 14 per cent; $\chi^2=10{\cdot}5$, d.f.$=1$, $P<0{\cdot}0002$). It is precisely these elderly groups of patients who have the highest mortality[6,8,13,14,16,18].

The use of a non-weighted medical risk factor score was originally shown to be correlated with mortality in patients with acute cholangitis[15]. The present study has confirmed the validity of this system when applied to all patients with CBD stones. Although there was no difference in mortality between any of the groups, patients in group 3 (ES only) were much older, with higher medical and total risk factor scores. For this reason the current policy of treating 'hish risk' patients by ES alone seems justified.

There is no doubt that outcome can be improved not only by a consideration of the technical aspects of surgery but by a realization that the use of ES has created new management problems. With regard to surgery, examination of several factors including the grade of surgeon, use of POC, type of operation and the presence of a single or multiple CBD stones had no statistical bearing on outcome. Reference to *Table 9* indicates some of the clinical and technical problems encountered in individual cases. The incidence of retained CBD stones following positive exploration was 10·9 per cent (9·1 per cent of all explorations). This compares with rates of 6–10 per cent reported by others[1,4–6]. Junior staff performed POC more frequently than consultants; there was no statistical relationship, however, between the incidence of retained stones and these grades of surgeons or the use of POC. Whereas POC was performed in 74 per cent, postexploratory cholangiography was performed in only 16 per cent. It can be argued that the need to clear completely the bile ducts of stones at operation is not as pressing as it once was given the relative safety of ES for this complication in the early postoperative period[19]. Nevertheless, two of the deaths in this series were associated with retained CBD stones (*Table 9*). We believe that greater attention should be given to clearing the ducts fully at operation and this should involve routine postexploratory cholangiography or choledochoscopy[2,3].

This study has shown that, when the CBD is not completely cleared of stones by ES at the initial attempt, the complication rate is significantly increased. In a recent prospective randomized study it was shown that pre-operative ES in non-high risk cases resulted in a greater overall incidence of complications compared with surgery alone[20] and this has been confirmed in the larger groups in this series. Although we would not recommend this approach routinely, it is applicable to patients with severe biliary acute pancreatitis and/or acute cholangitis[15,20–22] and to patients with a treatable intercurrent medical problem.

Failure of endoscopic stone extraction should prompt urgent reconsideration of management. One patient from group 1 (pre-operative ES) with failed ES died awaiting surgery (*Table 9*). Failure of ES in 'high risk' patients is fraught with even greater danger; although surgery may not be desirable, delaying surgery increases the hazards. Alternative non-surgical approaches including the use of nasobiliary catheters, wide bore endoprosthesis[23] and percutaneous cholecystostomy[24] must receive wider application. Four of the twelve deaths which occurred in groups 3 and 4 were associated with incomplete stone clearance without additional measures being employed (*Table 9*). The routine use of transnasal biliary catheters or large endoprostheses in cases of incomplete clearance may have reduced the mortality in this group. Outcome is not only related to the presenting condition; endoscopic manipulation of the biliary tree is associated with an increased rate of infection of the bile ducts[25] and the gallbladder[20]. Whereas the immediate risk from bile sepsis is greatly reduced if complete CBD clearance is achieved, the risks would appear to be increased if this is not achieved *ab initio*.

Where do we go from here? First, we would suggest that patients with CBD stones be treated by surgeons and endoscopists working closely together. Patients referred for therapeutic endoscopy must be managed along 'surgical' lines in the pre- and post-ES periods. Secondly, although systems of assessing risk need to be improved, those currently available along with medical risk factor scores need to be generally applied to allow better comparison of outcome between different series.

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Urological complications in 600 consecutive renal transplants

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The results of 600 consecutive renal transplant operations (540 cadaver and 60 living related donor) in 491 patients were assessed with respect to urological complications. In nearly all cases the ureter was inserted into the bladder using a Leadbetter–Politano ureteroneocystostomy technique. The bladder was drained by Foley catheter for 5 days and the operation site by vacuum drain for a variable period. After 26 operations in 26 patients, 27 episodes of ureteric obstruction were identified (one re-obstruction). These occurred between 1 day and 45 months after transplantation and involved the lowest third of the ureter 19 times, the middle third 3 times and the proximal third 4 times. They were due to stricture (11), pelvic collection (7), redundant or twisted ureter (3) or other cause (5). An anatomical predisposing factor in either patient or graft was identified in 31 per cent of these caes. After 18 operations in 18 patients, 21 episodes of urine leakage were identified (three re-leakages). These occurred between 1 day and 6 months after transplantation and an anatomical predisposing factor in either patient or graft was present in 59 per cent. Thus, overall, 7 per cent of patients developed a urological complication in this series. This rate has declined in recent years in parallel with a general reduction in steroid dose for immunosuppression. This last feature, combined with the surgical technique described, has resulted in a low incidence of urological complication after transplantation, being now between 1 and 2 per cent.

Keywords: Urological complications, renal transplant

Large contemporary series show that urological complications after renal transplantation continue to be a significant problem with an overall incidence of about 13 per cent[1,2]. Any complication in what is effectively a solitary kidney must be a cause for concern, but in the transplant situation additional factors exist which make urological problems particularly serious. Not only must they be distinguished from allograft rejection as a cause of impaired renal function, but also they occur in immunosuppressed patients who are particularly at risk from poor healing and inability to overcome local and systemic infection. The present series is a report of the urological complications encountered after 600 consecutive renal transplant operations from the inception of the Oxford Transplant Unit in 1975 up to 1986. Throughout this period the surgical technique in general, and the method of implanting the ureter into the bladder in particular, has remained unchanged. On the other hand the immunosuppression regimen has changed several times with one very significant change being the replacement of high dose with low dose steroid protocols[3]. This almost certainly has had a significant effect on the incidence of urological complications.

Patients and methods

Between January 1975 and September 1986, 600 consecutive renal transplant operations (540 cadaver and 60 living related donors) were performed on 491 patients of mean age 37·8 years (range 6–63 years). The male to female ratio was 1·7:1. These operations comprised 487 first transplants, 95 second, 15 third and 3 fourth transplants, and were carried out by a succession of consultants and senior registrars over the period of the study, all of whom were experienced in transplantation surgery. The follow-up to January 1987 (i.e. from 12 years to 4 months) is reported.

Over the 12 year period five basic immunosuppression regimens have been employed. Of the patients 171 were initially given high dose prednisolone (100 mg day^{-1}) and azathioprine 2·5 mg kg^{-1} day^{-1}; 194 low dose prednisolone (30 mg day^{-1}) and azathioprine 2·5 mg kg^{-1} day^{-1}; 102 cyclosporin 17·5 mg kg^{-1} day^{-1}; 38 cyclosporin 15 mg kg^{-1} day^{-1} and prednisolone 30 mg day^{-1}; 95 cyclosporin 10 mg kg^{-1} day^{-1}, azathioprine 1·5 mg kg^{-1} day^{-1} and prednisolone 20 mg day^{-1} (triple therapy). In the weeks following transplantation the immunosuppressive agents in all of these regimens were altered according to clinical circumstances but with an eventual reduction to low level maintenance doses by 6 months. Episodes of acute rejection were treated with 1 g methylprednisolone daily for 3 days in the early years and more recently by 0·5 g methylprednisolone daily for a similar period.

After revascularization of the kidney a primary ureteroneocystostomy was fashioned in 597 operations, which was the preferred technique for both normal and abnormal bladders. In two operations where the donor ureter was particularly short a uretero–ureterostomy was fashioned and at one procedure a submucosal implantation into a bladder caecoplasty was carried out. In all 597 instances in which a ureteroneocystostomy was performed, this was done using a modified Leadbetter–Politano technique[4]. The bladder was distended using 1 per cent neomycin solution injected via a Foley urethral catheter and an anterior cystotomy made. The ureter was brought into the bladder through a stab incision and led through a submucosal tunnel of about 3 cm length. The ureter was then trimmed to its final length, spatulated and secured by four 4/0 chromic catgut sutures after which the mucosal defect at the proximal end of the tunnel was closed with one or two further catgut sutures. An umbilical catheter was passed proximally via the completed ureteroneocystostomy into the renal pelvis to exclude problems such as twisting of the ureter or obstruction due to external compression. When the situation appeared satisfactory the catheter was withdrawn leaving the anastomosis unstented. The cystotomy was closed using two layers of absorbable suture, usually 2/0 polyglycolic acid (Dexon (Davis and Geck, UK)), and a vacuum drain placed alongside the vessels and ureter. After completion of the operation the Foley urethral catheter was retained for 5 days. The vacuum drain was removed at a variable time according to clinical circumstances but usually on the second postoperative day.

Renal function was monitored daily in all patients in the early period after transplantation by plasma creatinine levels and creatinine clearance. Routine imaging of the graft was not performed but B mode ultrasonography combined with Whitaker's test when clinically appropriate[5] and ^{99m}Tc diethylene triamine penta-acetic acid renography with diuretic provocation[6] were carried out at each episode

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of functional impairment of unknown cause. If these investigations suggested a urological complication the investigation of choice for definitive diagnosis was antegrade urography. Intravenous urography or ascending urography and cystography were performed only occasionally.

Statistical comparisons between groups were made using a χ^2 analysis with Yates's correction.

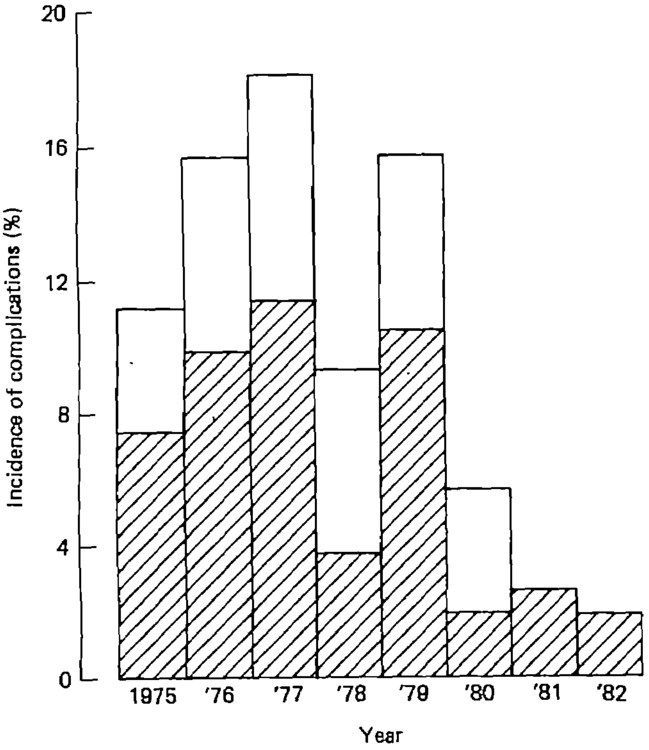

Figure 1 *Incidence of urological complications from 1975 to 1982 (minimum follow-up: 4 years).* □, *leakage;* ▨, *obstruction*

Table 1 *Urological complications and immunosuppressive regimens*

Regimen	Period of usage	Number of grafts	Number of primary complications (%)
High dose pred.+aza.	1975–79	171	26 (15·2)
Low dose pred.+aza.	1978–85	194	10 (5·2)
CyA*	1980–85	102	5 (4·9)
CyA+pred.	1983–85	38	1 (2·6)
CyA+aza.+pred.	1985–86	95	1 (1·1)
Total	1975–86	600	43 (7·2)

CyA, Cyclosporin A; pred., prednisolone; aza., azathioprine
* With conversion to aza.+pred. at 3 months after transplantation

Results

All urological complications identified after 600 consecutive transplant operations were due to either obstruction or leakage of urine. There were 43 (7 per cent) primary complications and 5 secondary complications (i.e. complications occurring after an attempt at correction of a primary complication). After 15 transplants in insulin dependent diabetics there were 3 urological complications but with such small numbers it was not possible to demonstrate that the 20 per cent incidence of urological problems in this group was statistically greater than that found in the non-diabetic population. Second, third and fourth transplant procedures were not associated with a greater incidence of urological complications than first transplants. All urological complications were successfully corrected and no graft loss or mortality was directly attributable to either the complication or the appropriate corrective measures.

Over the period of the study the complication rate has declined markedly. The vast majority of complications occurred within a few months after transplantation; that most distant to the time of operation was an episode of obstruction at 45 months. With a follow-up of at least four years after operation the incidence of complications fell from 11 per cent in 1975 to 2 per cent in 1982 (*Figure 1*) and, with a shorter available follow-up, this low value has been maintained up to the present day. No change occurred in the operative management during this period and in particular the technique of ureter to bladder anastomosis was constant. The most obvious change in general management over the study period was a reduction in the dosage of steroid used both in routine immunosuppressive protocols and for the treatment of episodes of rejection. The incidence of complications associated with five immunosuppressive regimens is described in *Table 1* and, although certain regimens have been in use for a relatively short time with a consequent reduction in follow-up period, it seems clear that the high steroid doses of earlier years were associated with a high rate of urological complications.

Obstruction

After 600 transplant operations 26 (4·3 per cent) primary episodes of obstruction occurred. After attempted correction there was one further (secondary) obstruction and one (secondary) urine leak. Site, time of onset and cause of obstruction are described in *Table 2*. Most obstructions occurred within 4 months of transplantation (range 4 h to 45 months) and were due to technical factors when they occurred early and to external compression or ureteric ischaemia when they occurred at a later time. While it has been suggested that ureteric ischaemia may sometimes be due to the rejection process, in the present series it was not associated with any statistically significant increase in the number or severity of rejection episodes. A possible predisposing factor for obstruction existing at the time of surgery was recognized in eight cases: difficult access to bladder (three), ischaemic ureter

Table 2 *Site, cause and time of diagnosis of 26 ureteric obstructions after 600 renal transplant operations*

Ureteric level	Cause (number of grafts affected)	Time after transplantation
Proximal third	Pelvi-ureteric junction obstruction (1)	3 months
	Double pelvis (1)	3 months
	Compression by lower polar artery (1) and lower pole of kidney (1)	4 and 6 months
Middle third	Redundant kinked ureter (2)	2 and 45 months
	Twisted ureter (1)	4 h
Distal third	Extravesical stricture (8)	6 days to 28 months
	Intramural stricture (3)	1 day to 10 weeks
	Compression by lymphocele (6)	3 weeks to 18 months
	Compression by abscess (1)	21 months
	Compression by inferior epigastric artery (1)	3 days

Table 3 *Nature and time of diagnosis of 17 urine leaks after 600 transplant operations*

Nature of leak (No. of grafts affected)	Time after transplantation (days)
Cystotomy (4)	9–63
Ureterovesical anastomosis (4)	1–25
Ureteric sloughing (8)	3–180
Ureteric pressure necrosis by spermatic cord (1)	8

(two), missed bifid pelvis (one), missed pre-existing pelvi-ureteric junction obstruction (one) and ureteric compression by lower polar renal artery (one). Of the 26 patients who developed a urological obstruction, 17 are alive with the same functioning graft and 3 are alive but retransplanted after graft failure due to rejection. Six have died (four with functioning grafts) but in no case was graft loss or death due to the urological obstruction or its management.

Urological obstruction was managed in all cases by revisional surgery including one in which there was an initial unsuccessful attempt made at percutaneous balloon catheter dilatation of an extravesical ureteric stenosis. Complications involving stricture of the ureter, either extravesical or intramural, were corrected by excision of the affected segment followed by Leadbetter–Politano ureteroneocystostomy (usually) or uretero-ureterostomy (rarely). Pelvi-ureteric junction obstruction was managed by pyeloureterostomy and bifid pelvis by pyeloplasty. Obstruction due to compression from adjacent structures such as arteries or the lower pole of the kidney was corrected by simple dissection to free the ureter whereas that due to compression from lymphocele was corrected by repeated percutaneous drainage of the lymphocele with or without subsequent operative fenestration of the lymphocele with the peritoneal cavity as necessary.

Urine leakage

After 600 transplant operations 17 (2·8 per cent) primary episodes of urine leakage occurred. After attempted correction there were three further (secondary) leaks and one (secondary) leakage occurred after surgery for ureteric obstruction. The nature and time of diagnosis are described in *Table 3*. No episode of urine leakage was recorded later than 6 months after transplantation. Those which occurred early were often due to technical factors while those more distant to the transplant operation were due to ischaemia or rejection affecting the ureter. Although bladder function was not routinely assessed, problems related to the bladder were considered to be possible predisposing factors for leakage in eight recipients: small scarred bladder with friable mucosa (four), cystitis cystica (one), megacystis from Marfan's syndrome (one), gross bladder hypertropy (one) and caecoplasty to tuberculous bladder (one). Predisposing factors related to the graft were skeletonized ureter (one) and lower pole artery anastomosed to inferior epigastric artery with subsequent thrombosis (one). Of the 17 patients who developed a urine leak, 6 are alive with the same functioning graft, 2 are alive but retransplanted after graft failure due to rejection and 3 are alive on dialysis, again after graft failure due to rejection. Six patients have died (three with functioning grafts) but in no case was graft loss or death due to the urine leakage or its management.

Conservative management was employed for six episodes of primary and one episode of secondary urine leakage. All four instances of leakage from the cystotomy were thus treated using bladder drainage by urethral catheter for a prolonged period (up to 31 days) but at the cost of three wound infections, one of which required operative drainage. Two instances of early leakage from the Leadbetter–Politano tunnel were managed successfully by leaving the vacuum drain in place for an extended period (up to 20 days) as was one secondary leak from a uretero-ureterostomy. In this final case when the drain was eventually removed a controlled cutaneous fistula resulted which eventually closed 3 months later.

The remaining 11 primary and 3 secondary leaks were managed surgically. Simple leakages were corrected by reconstruction of the ureteroneocystostomy usually with an indwelling stent and this was also the preferred technique in cases of limited necrosis or sloughing of the ureter. However, if ureteric necrosis was extensive, resulting in a short ureter after excision of the damaged segment, a stented pyelo-ureterostomy (usually) or a stented uretero-ureterostomy (one one occasion only) was fashioned. In recent years, stenting at revisional procedures has been carried out using indwelling double-J stents which were removed at cystoscopy a few weeks later.

Discussion

While relatively small series of patients have been reported with widely different incidences of urological complications, ranging from 0·9 per cent[7] to 29·6 per cent[8], the largest modern series suggest an incidence of about 13 per cent[1,2]. While many factors play a part, we believe that two are of outstanding importance and merit special comment.

Firstly, it is clear that many urological complications are of technical origin and the constant surgical technique used in the present large series which has been associated with a relatively low rate of urological problems (7 per cent) is, therefore, of interest. The need for care in removal of any kidney used for transplantation is well recognized and in the present context it is important that the ureteric blood supply be protected as far as possible[9]. Skeletonization of the ureter is likely to result in ischaemia and subsequent urological problems. A variety of techniques have been advocated for ureterovesical anastomosis[4,10,11] but that of Politano and Leadbetter has proved very satisfactory in our experience. Most surgeons leave a urethral Foley catheter inserted in the transplant recipient's bladder for a variable period and we have found that its removal routinely on the fifth postoperative day is attended by few problems. Drainage of transplant wounds is not universally advocated[1,12] but in the present series it has never been obviously related to any complication and we feel that vacuum drainage can be advocated as a routine measure.

The second factor of importance is immunosuppression and particularly the use of steroids. The incidence of urological complications, both obstruction and leakage, has fallen in the Oxford Transplant Unit over the years to less than 2 per cent (with a 4 year follow-up) in 1982. This low incidence has been maintained, although obviously with a shorter follow-up, to the present day. In the early years a high dose steroid immunosuppressive regimen was employed but from 1980 this was superseded by a variety of low dose steroid protocols. From this time onward (*Figure 1*) the rate of urological complications fell dramatically with an annual incidence of only 3·5 per cent (2·3 per cent obstruction and 1·2 per cent leakage) for the 7 years to 1986 compared with an annual incidence of 14·0 per cent (8·6 per cent obstruction and 5·5 per cent leakage) for the 5 years before 1980. Without any other significant change in the routine management of patients after transplantation to explain the fall in urological complications, the case against high dose steroid protocols is substantial.

When it is recognized, ureteric obstruction must be managed aggressively if function is not to be irretrievably lost. While some have advocated the use of percutaneous balloon dilatation in certain circumstances, the long-term outcome of this measure remains uncertain even if initial success is achieved. In Oxford, obstruction has in general been managed by revisional surgery which has always been accompanied by some improvement in renal function. It should be noted, however, if obstruction has been long-standing, that functional retrieval may be minimal and in any event is likely to be less pronounced than that seen after surgery in the early acute obstructive situation. While routine ultrasonography and isotope renography are probably unwarranted, if functional impairment not obviously due to rejection or cyclosporin toxicity is encountered, these tests should be performed without delay. Technical advances in isotope renography and especialy in ultrasonography have undoubtedly helped in the early diagnosis of obstruction and revisional operations now benefit from the availability of indwelling ureteric double-J stents.

Urine leakage may be handled with success by conservative means although subsequent infection can be troublesome. The decision not to proceed with revisional surgery should not be taken lightly, despite today's low steroid regimens and modern antibiotics. While in the past a definitive diagnosis of leakage was usually obtained by intravenous urography or cystography, it is our experience that modern techniques such as antegrade pyelography under ultrasonographic control are most helpful diagnostically and indwelling stents assist the safe surgical correction of leakage.

This retrospective analysis has demonstrated that the technique of Leadbetter–Politano ureteroneocystostomy, with Foley catheter drainage of the bladder and vacuum drainage of the extravesical tissues, is attended by a low rate of urological complications, especially in the era of low steroid immunosuppression. Early diagnosis of urological problems, should they occur, is possible using one or more of the techniques described and revisional surgery for such complications is likely to be met with success in terms of improved renal function. In the present series this surgery has not been responsible for graft loss nor has it been associated with any patient mortality.

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Prospective assessment of carotid endarterectomy by clinical and ultrasonic methods

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Sixty-three carotid endarterectomies in 60 patients were followed by clinical and duplex scanning at 2 weeks postoperatively and at 3-monthly intervals for 3 years (mean 18 months). Four patients died (two of stroke, two of myocardial infarction) and four survivors had recurrent ipsilateral symptoms. Two had an immediate mild hemiparesis which recovered completely within 36 h; in both, the endarterectomized arteries were patent on scanning. The other two experienced amaurosis fugax for 2–3 weeks at 2 and 24 weeks; scanning showed that the sites of both endarterectomies had become occluded. Ultrasound assessment at 2 weeks showed that 43 of 61 (70·5 per cent) endarterectomized arteries were widely patent. There were three occlusions, one stenosis of >75 per cent, three stenoses of >50 per cent and eleven stenoses of <50 per cent. At 6 months a total of five vessels were occluded, with >75 per cent stenosis in three and >50 per cent stenosis in eight. At latest follow-up, six of eight arteries with >50 per cent stenosis shown earlier had scans which had reverted to normal. Tacking down of the distal intima was associated with higher incidence of restenosis and occlusion (P<0·01). Women were more predisposed to restenosis by neointimal hyperplasia (P<0·05). All restenosis occurred within the first 6 months postoperatively (26·2 per cent) and fell to 16·4 per cent at the end of the study.

Keywords: Carotid restenosis, duplex scanning, spectral broadening

Although the clinical results of carotid endarterectomy are reasonably well documented[1,2], the actual rate of restenosis is unknown since arteriography is seldom justified. The incidence is said to range from 1–3·6 per cent in patients with recurrent symptoms[3–5], to 10–36 per cent in screening studies[6–11]. The results depend upon the timing, frequency and sensitivity of the investigative method. Carotid restenosis results from technical error[7,12,13], neointimal hyperplasia[3,4,12] or progression of atherosclerosis[3,4,12]. In this prospective study an early, frequent and regular assessment of carotid endarterectomy was performed by clinical and duplex scanning methods.

Patients and methods

Sixty consecutive patients, 46 men and 14 women, with a mean age of 62 years underwent 63 carotid endarterectomies between March 1982 and March 1985. All took 300 mg of aspirin daily. They were examined clinically and by duplex scanning at 2 weeks and at 3-monthly intervals to 3 years (mean 18 months). The indications for surgery are given in *Table 1*. Pre-operative triplanar carotid angiography was performed in 58 patients. Severe stenosis of >75 per cent reduction in luminal diameter was found in 39 patients, 50–75 per cent stenosis in 15, and <50 per cent stenosis with ulceration in 4 patients. Three operations were performed in two patients without angiography because duplex scanning showed a clearcut severe stenosis.

During the operation 5000 units of heparin was invariably given intravenously before clamping and was not later reversed. An intraluminal shunt was used in 21 of the operations depending on the stump pressure and the severity of contralateral carotid disease. Laterally, shunting was invariably done. In 18 operations (28·6 per cent) the distal intima was tacked down by 2–3 stitches of 6/0 Prolene (Ethicon Ltd, UK). A vein patch was used to close the arteriotomy in four operations because the distal artery was hypoplastic.

At postoperative follow-up, a standard interview was used to determine the occurrence and timing of any recurrent cerebrovascular symptoms, cardiovascular status, associated risk factors, current smoking habits and aspirin therapy. The assessment was completed by auscultation for carotid murmur. An ultrasound scan of the extracranial carotid arteries was performed bilaterally using a Mark 500 ATL duplex scanner (Advanced Technology Laboratories, Squibb Medical System Limited), with a 5 MHz short focus pulse Doppler flowmeter and 7·5 MHz real time, B-mode imager. Five categories of results were identified according to peak systolic and diastolic frequencies and spectral broadening of the Doppler shift signal (*Table 2*). In 109 patients, duplex scans and triplanar angiographies correlated well with a sensitivity of 98·8 per cent, specificity of 90 per cent and $\kappa = 0{\cdot}854 \pm 0{\cdot}026$.

κ statistic corrects for chance agreement and is calculated according to the formula:

$$\kappa = \frac{P_o - P_c}{1 - P_c}$$

where P_o = observed agreement and P_c = calculated chance agreement. The value of κ is equal to zero if the observed agreement is equivalent to that reached by chance alone. A perfect agreement reaches a maximum value of +1 and an inverse correlation will give a value of κ less than zero[14].

Table 1 *Indications for carotid endarterectomy (63 operations)*

Symptoms	Number of operations
Transient ischaemic attacks (TIAs)	28
Amaurosis fugax	18
Reversible ischaemic neurological deficit (RIND)	5
Asymptomatic carotid murmur	4
Minor stroke	3
Ipsilateral permanent partial blindness	3
Contralateral permanent complete blindness	1
Non-lateralizing symptoms	1

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Table 2 *Classification of post-endarterectomy internal carotid artery velocity pattern*

Category	Velocity pattern criteria
A: Normal	Systolic peak frequency up to 4 kHz. No spectral broadening in systole
B: < 50% stenosis 'Flow disturbance'	Systolic peak frequency up to 4 kHz. Marked spectral broadening throughout systole
C: > 50% stenosis 'Soft' and 'harsh' high velocity signal	Systolic peak frequency above 4 kHz with or without spectral broadening
D: > 75% stenosis	Systolic peak frequency above 7·5 kHz, marked spectral broadening throughout systole. Diastolic frequency above 4 kHz
E: Occlusion	No signal in internal carotid artery with absent pulsation. No diastolic flow in the common carotid artery, enhanced flow in the external carotid

Table 3 *The incidence of carotid restenosis and occlusion in 61 endarterectomized arteries*

	Degree of restenosis				
Period	< 50%	> 50%	> 75%	Occluded	Total
2 weeks	11	3	1	3	29·5%
6 months	0	8	3	5	26·2%
Last follow-up	0	2	3	5	16·4%

Results

Clinical assessment

Perioperative cerebrovascular complications. Two patients recovered from anaesthesia with dense hemispheric strokes related to the site of the operation and died at 3 days and 3 months postoperatively. Difficulties had been encountered during insertion of the shunt in both patients with extensive atherosclerosis. The results of autopsy in the first patient, and computerized tomography (CT) and duplex scanning in the second patient, revealed infarcted areas in the ipsilateral parieto-occipital region with patent endarterectomized arteries.

Two patients developed an immediate mild hemiparesis which recovered completely within 36 h. In both the endarterectomized arteries were widely patent during follow-up.

Postoperative cerebrovascular symptoms. Two patients in whom the endarterectomized arteries became occuluded at 2 and 24 weeks experienced amaurosis fugax from 2–3 weeks. Contralateral symptoms occurred in three patients in whom pre-operative carotid angiograms had shown < 50 per cent stenosis of the internal carotid artery in the newly symptomatic side. On subsequent follow-up at 15, 27 and 36 months respectively, they were symptom-free without any deterioration of their arteries.

Two patients died of myocardial infarction during follow-up at 12 and 21 months. Both had been free of cerebrovascular symptoms and carotid restenosis.

Ultrasound assessment

The results of duplex scanning of 61 endarterectomized arteries are shown in *Table 3*. Ultrasound testing at 2 weeks showed that 43 were normal (*Figure 1*), three arteries were occluded, one had > 75 per cent stenosis (*Figure 2*), three had > 50 per cent stenosis (*Figure 3*) and eleven had flow disturbances amounting to < 50 per cent stenosis. At 6 months four of eleven arteries with < 50 per cent stenosis had returned to normal, three progressed to > 50 per cent stenosis, two developed > 75 per cent stenosis, and two became occluded. Two of the arteries with a normal scan at 2 weeks showed > 50 per cent stenosis at 6 months. At latest review, scans of six of eight arteries with > 50 per cent stenosis had reverted to normal.

Ultrasound criteria for carotid stenosis before endarterectomy were not always appropriate for postoperative restenosis. For example, *Figure 4* shows (arrowed) smooth narrowing of the carotid bulb at 6 months. The Doppler peak systolic frequencies of 6000 Hz would pre-operatively suggest > 50 per cent stenosis. However the signals show a clear window below peak systole, which is seen in laminar flow without turbulence, and in this case studies at 18 months showed a return to normal peak frequencies (< 4000 Hz).

Predisposing factors

Distal intima was tacked down in 10 of the 16 arteries which developed > 50 per cent stenosis or occlusion compared with 8 out of 45 arteries in which there was no evidence of restenosis (Fisher's exact test = 0·003; $P < 0{\cdot}01$). Six of the sixteen restenosed or occluded arteries occurred in female patients (Fisher's exact test = 0·034; $P < 0{\cdot}05$). Of these six arteries, three had > 50 per cent stenosis at 6 months scanning and had reverted to normal at the latest follow-up. No restenosis occurred in the patients with vein patch closure of the endarterectomy. There was no difference between the two groups (patent and restenosed arteries) regarding other risk factors such as age, hypertension, diabetes, smoking habits, cardiovascular status, peripheral vascular disease and pre-operative severity of carotid disease in the operated and unoperated sides.

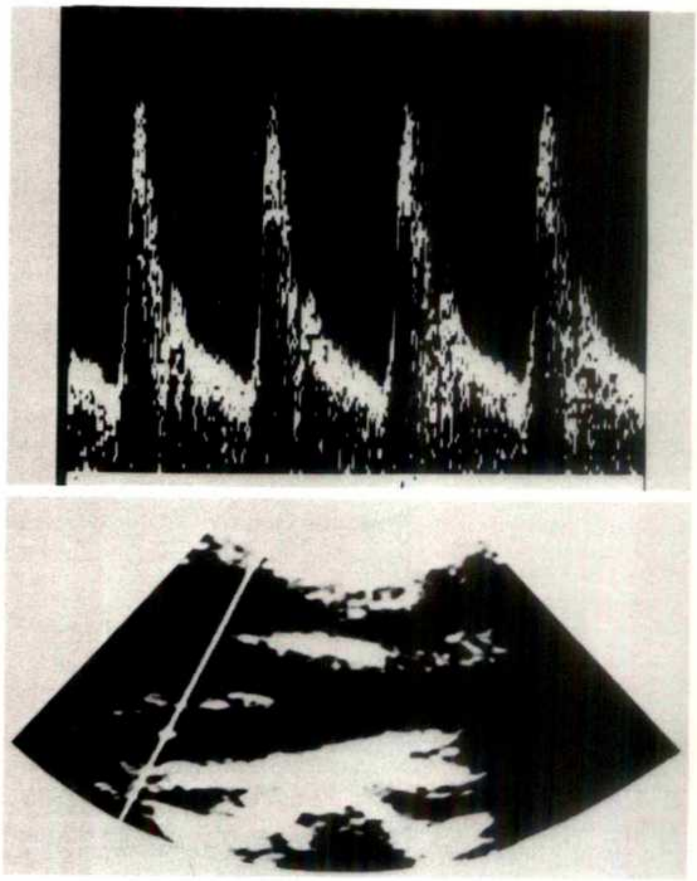

Figure 1 *Normal carotid scan 2 weeks post-endarterectomy. Note the normal peak frequencies (3440 Hz) and the presence of a smooth unconstricted lumen of the bifurcation*

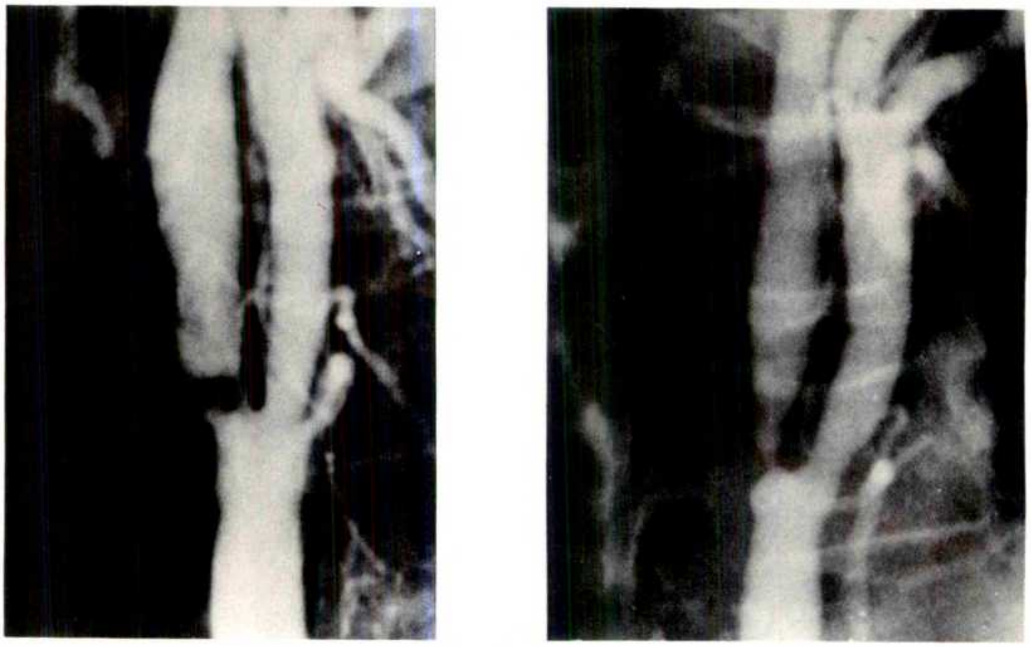

Figure 2 *Arteriograms showing (left) pre-operative severe eccentric atheromatous stenosis and (right) 1 year post-endarterectomy, a smooth concentric restenosis from neointimal hyperplasia*

Discussion

Technical factors are a major cause of carotid restenosis[7,12,13]. Incomplete removal of the distal extent of the atheromatous plaque, distal flap, proximal step, medial tags, vascular clamp damage and suture faults, particularly at the distal end of the arteriotomy, can lead to a disturbance in laminar flow and may enhance neointimal hyperplasia and retard re-endothelialization[13].

In this study the distal intima was tacked down in 10 of 16 arteries which showed >50 per cent restenosis or occlusion, compared with only 8 of 45 without restenosis ($P < 0.01$, Fisher's exact test). Salvian *et al.*[7] studied 105 carotid endarterectomies by oculopneumoplethysmography and reported an 11·4 per cent incidence of carotid restenosis. In 75 per cent of the arteries in which restenosis developed the operative details revealed a problem with the distal end of the endarterectomy, notably incomplete feathering of the plaque and tacking down of distal intima. The high rate of tacking down distal intima could be due to an incomplete endarterectomy, the endarterectomy plane being too deep, or to atheroma being insufficiently localized. Every effort is now made to extend the arteriotomy beyond the distal end of the plaque. Since then very few distal intimal sutures have been needed.

Immediately following endarterectomy a compliance mismatch may occur between the soft endarterectomized segment and the relatively stiff adjacent artery. This could result in alteration in blood vessel geometry and produce temporary flow disturbances, since some abnormalities disappeared on repeat scanning. Recently Ackerstaff *et al.*[15] found that the majority of endarterectomized arteries with minimal or mild spectral broadening at 3 months postoperatively either disappeared or remained stable during the follow-up. Russell *et al.*[16] used spectral analysis of Doppler signals and intravenous digital subtraction angiography (DSA) to follow up 60 endarterectomized arteries. Spectral broadening was identified in 52 per cent of arteries, while DSA showed wall irregularities in only 25 per cent.

Regarding haemodynamically significant carotid restenosis (>50 per cent), duplex scanning has been reported to produce the highest incidence[10,11]. Zierler *et al.*[11] used completion angiography to document the technical results of their operations. In spite of that they found that up to 36 per cent of the endarterectomized arteries were restenosed at >50 per cent in 89 operations, reducing to 19 per cent at the end of their follow-up (mean of 16 months). In the present study the incidence of >50 per cent restenosis was 26·2 per cent at 6 months follow-up, reducing to 16·4 per cent at the end of the study (mean of 18 months), while other non-invasive tests have been reporting only 10–12·5 per cent[6–9]. Roederer *et al.*[17] compared the results of duplex scanning with the results of multiplanar angiograms following 44 carotid endarterectomies. Of the arteries which were diagnosed by angiography to have <50 per cent restenosis, 19 per cent were overestimated by spectral analysis and placed in the category of >50 per cent stenosis.

During our study we felt that duplex scanning might overestimate the diagnosis of >50 per cent stenosis. This is because some of the Doppler signals did not fit Strandness's[10,11] pre-operative criteria of >50 per cent stenosis in the sense that they did not have spectral broadening. This could be due to the smooth subcritical narrowing from neointimal hyperplasia (*Figure 4*). Some of these signals could have arisen from other haemodynamic changes like augmentation of flow in small internal carotid arteries. Similar signals have been observed in patients with occluded contralateral internal carotid artery, in A–V malformation and in patients on haemodialysis.

We classified these high velocity signals into two types, 'soft' and 'harsh'. Soft signals were found in two specified cases: (i) augmented flow in the internal carotid artery and (ii) neointimal hyperplasia with a smooth stenosis and laminar flow (*Figure 4*). Harsh signals were always associated with turbulent flow (*Figure 3*) and a stenosis of >50 per cent. However, postoperative angiography has not been used routinely.

In this study all restenoses and occlusions occurred within the first 6 months because of technical errors[7,12,13] and neointimal hyperplasia[3]. Women were more predisposed to restenosis by neointimal hyperplasia probably because of different platelet responses and smaller sized arteries[10,18]. There may be a case for closing the arteriotomy with a vein patch in female patients with a small internal carotid artery.

In summary, we report a 3·3 per cent rate of symptomatic carotid restenosis and a 16·4 per cent rate of asymptomatic restenosis at the end of the study. Once restenosis has been diagnosed, careful thought has to be given to management.

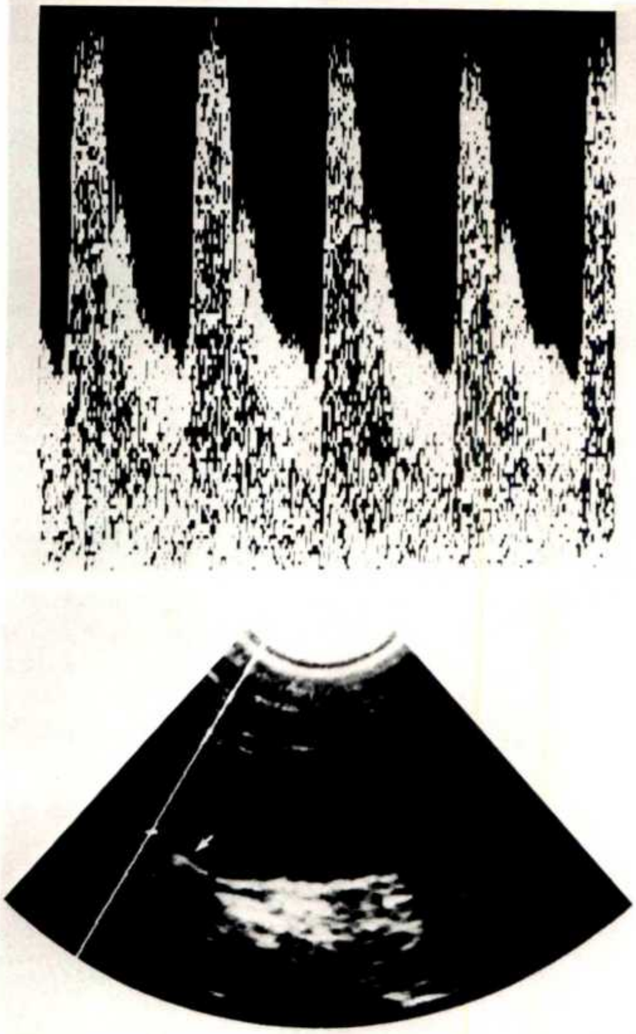

Figure 3 *Restenosis shown by ultrasound scan 2 weeks after carotid endarterectomy. Note the high peak systolic frequencies (8640 Hz) with marked spectral broadening ('harsh' signal). The arrow in the lower image shows incompletely feathered atheroma at the distal margin of the endarterectomy*

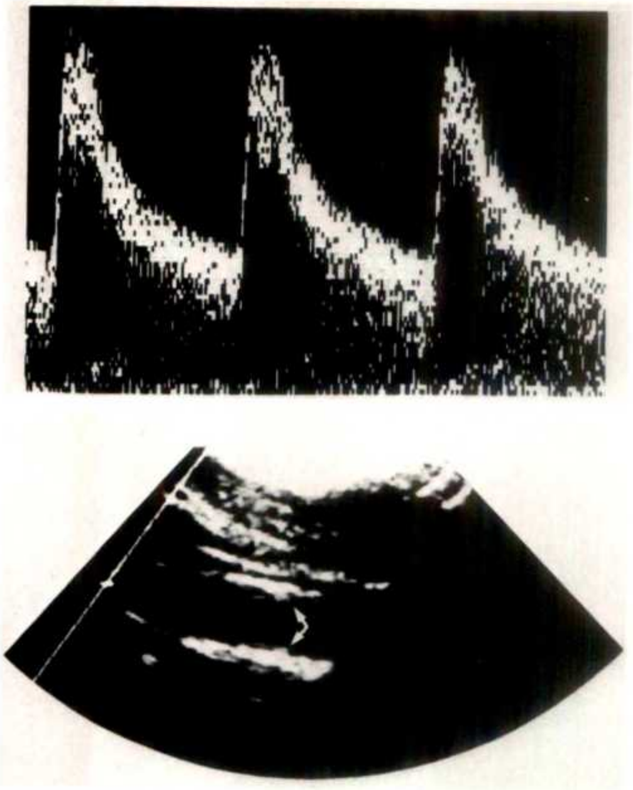

Figure 4 *Carotid scan 6 months post-endarterectomy showing smooth neointimal hyperplasia (arrowed). Despite the raised peak systolic frequencies of 6000 Hz, flow was laminar with a clear window below systole showing the absence of turbulence ('soft' signal). Later the peak frequencies returned to normal (see text)*

Most patients require no treatment. A few with persistently troublesome focal symptoms may need to be considered for reoperation.

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Experience with the 'skew flap' below-knee amputation

A review of 353 lower limb amputations over the last 7 years has been performed to assess the results of the skew flap myoplastic below-knee amputation which was introduced in April 1983 because of reported advantages in terms of wound healing and earlier ambulation. Comparing the first 3½ year period with the second, the total number of amputations decreased by 31 per cent. The number of above-knee amputations remained similar in the two periods (82, 62), whilst the number of Gritti–Stokes amputations fell from 79 to 21 (0·001 > P > 0·01). The proportion of below-knee (BK) amputations increased from 50 (23·7 per cent) to 59 (41·5 per cent) (0·01 > P > 0·025). The groups were comparable in terms of previous vascular surgery and co-existing medical conditions. The time to full stump healing was significantly shorter in the skew flap group compared with the earlier Burgess type BK amputation (P = 0·001), and there was a trend to fewer stump failures in the skew flap group. We therefore feel that the skew flap amputation gives superior results to the Burgess BK amputation in terms of healing and a lower complication rate, allowing a higher proportion of BK amputations to be performed. A prospective randomized trial of the two techniques is in hand to determine the accuracy of this hypothesis.

Keywords: Below-knee amputation, skew flap, Burgess long posterior flap

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Advances in arterial bypass surgery over the past 20 years have resulted in the salvage of many limbs which would otherwise have required an amputation, but there inevitably remains a group of patients in whom vascular reconstruction is not possible, or whose fulminating lower limb infection requires an amputation to relieve pain or save life.

The choice of amputation level depends upon many factors but, providing there is no contraindication, there is general agreement amongst surgeons and prosthetists that a below-knee amputation is the procedure of choice[1]. Failure of healing is more common with the Burgess below-knee amputation than with more proximal procedures except through-knee amputations. Because of reported superiority in wound healing and early ambulation[2], the 'skew flap' myoplastic below-knee amputation was adopted in Derby. The purpose of this study is to assess the results of below-knee amputations in two 3½ year periods before and after the introduction of the skew flap below-knee amputation.

Patients and methods

A retrospective review of major lower limb amputations in Derby between October 1979 and October 1986 was performed, taking April 1983 as the dividing point for the two 3½ year periods as it was then that the skew flap (SF) below-knee amputation was adopted.

In the first period 211 amputations were performed, and in the second 142. The indication for surgery was irrevocable ischaemia in the majority, diabetic gangrene being responsible for the remainder. There was no significant difference between the long posterior flap (LPF) and the skew flap (SF) groups with respect to the incidence of diabetic gangrene.

The case notes were analysed for patient's age, previous vascular surgery, co-existing medical conditions, indications for surgery, operation performed and operative mortality. Operative mortality is defined as death occurring within 30 days of the most recent operation. A commonly employed method of comparing the results of amputations is to look at the length of time spent in hospital in each of the groups. In our study a random sample of 75 cases was examined for correlation between length of hospital stay and time to full healing, and comparing these measurements, the Spearman Coefficient was 0·212 (n.s.), showing a poor degree of correlation between the two values (*Figure 1*). As we were most interested in wound healing it was this that was recorded.

Statistical analysis

The Mann–Whitney U and the χ^2 tests were employed where appropriate to analyse the data for evidence of statistically significant differences between groups. Statistical significance was inferred at the 5 per cent level.

Results

The age and sex distribution in each group was comparable (see *Table 1*).

Previous vascular procedures had been performed in 22 (30·9 per cent) of the LPF group and 27 (71·1 per cent) of the SF group (*Table 2*). The commonest procedure in each group was chemical sympathectomy. Contralateral amputation had been performed in a total of 26 cases (7·4 per cent overall).

Co-existing medical conditions often increase morbidity, but in our series the presence of one or more 'risk factors' had no significant effect on mortality. There was no difference between the LPF and SF groups with respect to risk factors. The risk factors indicated in *Figure 2* are diabetes mellitus, cardiovascular disease, cerebrovascular disease and chronic obstructive airways disease.

Time to full stump healing was significantly shorter in the SF group compared to the LPF amputations ($P = 0·001$). Stump

Table 1 *Clinical details of patients*

	AK	GS	LPF	SF
1979–1983				
$n = 211$	82	79	50	0
Median age	73·5	73·0	72·5	
Range	(42–93)	(45–99)	(40–96)	
Sex (M/F)	46/36	46/33	30/20	
1983–1986				
$n = 142$	62	21	21	38
Median age	75·0	75·0	74·0	74·0
Range	(49–93)	(49–92)	(42–96)	(42–96)
Sex (M/F)	33/29	15/6	13/8	25/13

AK, above-knee amputation; GS, Gritti–Stokes amputation; LPF, long posterior flap below-knee amputation; SF, skew flap below-knee amputation

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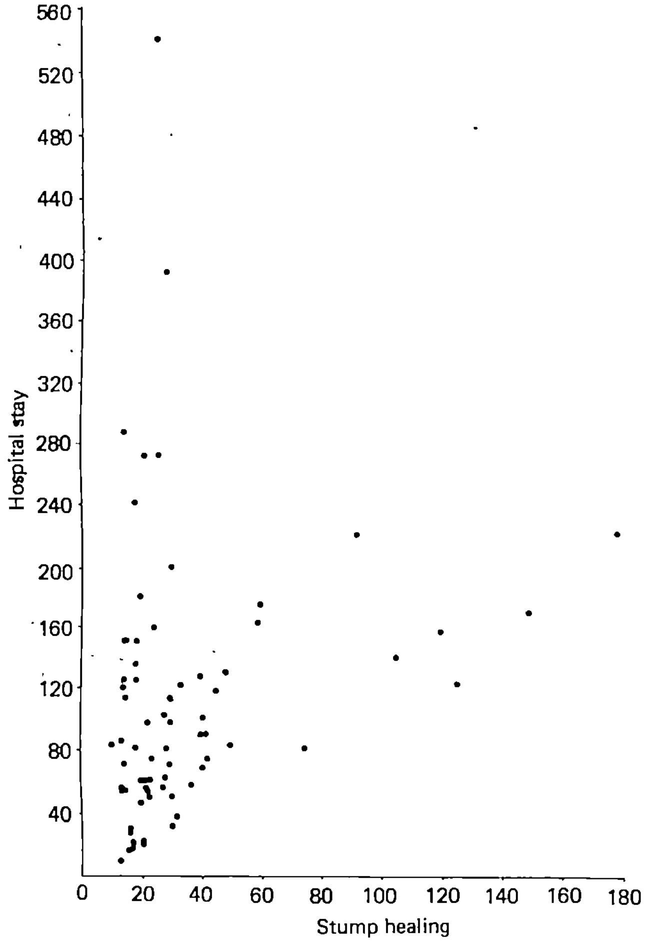

Figure 1 *Correlation between length of hospital stay and time to full healing*, r=0·212

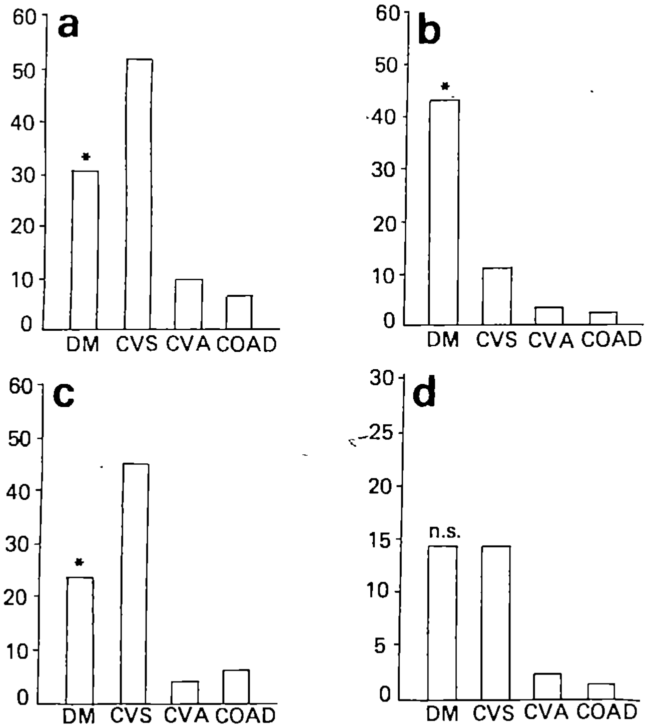

Figure 2 *Mortality with respect to the presence of risk factors.* **a** *Above-knee amputation, n=144;* **b** *long posterior flap below-knee amputation, n=71;* **c** *Gritti–Stokes amputation, n=100;* **d** *skew flap below-knee amputation, n=38. DM, Diabetes mellitus; CVS, cardiovascular disease; CVA, cerebrovascular disease; COAD, chronic obstructive airways disease. *P=0·01; n.s.=no statistical significance*

Table 2 *Previous vascular procedures*

	LPF (*n*=71)	SF (*n*=38)
Chemical sympathectomy	13	8
Surgical sympathectomy	0	0
Proximal graft	2	2
Femoropopliteal bypass	4	7
Embolectomy	0	3
Angioplasty	0	2

Table 3 *Stump healing*

Time to full healing (days)	LPF	SF
Median	26·0*	16·5*
Range	(14–184)	(13–110)
AK conversion	8 (11·32%)†	2 (5·26%)†

* *P*=0·001
† n.s., No statistical significance

failure requiring conversion to an AK amputation occurred in only 5·3 per cent of skew flap amputations compared to 11·3 per cent in the Burgess long posterior flap amputations, although this just failed to reach statistical significance (see *Table 3*).

There was no significant difference between the operative mortality in the LPF group (4/21 patients) and the SF group (3/38 patients) during the period 1983–86.

Discussion

Our experience shows that the rate of primary healing is significantly better following a skew flap amputation than after a Burgess long posterior flap^3 below-knee amputation, allowing a higher proportion of below-knee amputations to be performed with a trend toward fewer stump failures. There was a significant increase in the number of BK amputations performed in 1983–86 as compared to 1979–83, which was mainly due to performing a high proportion of the skew flap procedure.

A theoretical disadvantage of the skew flap amputation is the difficulty encountered when a previous femorodistal bypass has been performed, as the incorporation of the previous wound results in unequal flaps. This is solved by 'gathering' the larger posteromedial flap, and in practice we did not find this a problem.

A randomized trial of skew flap against long posterior flap below-knee amputations is in hand to determine the accuracy of our hypothesis that the skew flap procedure produces superior results in terms of wound healing and rehabilitation from amputation.

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Defective fibrinolysis: a risk factor in early femoropopliteal graft thrombosis

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Resting plasma fibrinolytic activity and fibrinolytic activity after stimulation by 10 min of venous occlusion (fibrinolytic potential) were estimated in 51 patients before femoropopliteal reconstructive surgery. Twelve patients suffered a graft thrombosis in the first month. Resting plasma fibrinolytic activity was similar in patients with thrombosed grafts and those with functioning grafts. However reduced fibrinolytic potential was found to be a risk factor for graft thrombosis in the month after surgery ($P = 0{\cdot}01$)*. Other risk factors were increasing age* ($P = 0{\cdot}007$) *and the indication for surgery* ($P = 0{\cdot}03$)*. Thirty-four patients whose grafts were functioning after 1 month were followed up for a mean of 9 months. A further eight grafts thrombosed. Neither fibrinolytic activity nor fibrinolytic potential were found to be risk factors for late graft thrombosis. Fibrinolytic potential has been shown to be an independent risk factor for early graft thrombosis. Peri-operative fibrinolytic stimulation might be a method of improving femoropopliteal graft patency.*

Keywords: Fibrinolysis, vascular reconstruction, graft thrombosis

It has been suggested that there is a balance between the production of intravascular fibrin due to endothelial wear and tear and its removal by the fibrinolytic system[1]. Alteration of this 'haemostatic balance' may predispose to thrombosis[2]. Defective fibrinolysis has been established as a cause of venous thrombosis in both retrospective[3,4] and prospective[5] studies. Abnormal plasma fibrinolysis in arterial thrombotic disease has also been demonstrated in studies of patients with claudication[6–8] and ischaemic heart disease[9,10]. Decreased fibrinolytic activity has been discovered in atherosclerotic arteries compared with macroscopically normal arteries from the same patient[11]. We have previously demonstrated reduced plasma fibrinolytic activity in patients who suffered an acute peripheral arterial thrombosis[12], though it still remains uncertain whether this was cause or effect. Prospective studies to determine whether reduced fibrinolytic activity is a risk factor for accelerated progression of atherosclerosis have yet to be performed.

Plasma fibrinolytic activity may be estimated from the euglobulin lysis time (ELT)[13]. Release of plasminogen activator from the vessel wall can be stimulated by venous occlusion and the increased fibrinolytic activity, measured as a reduction in ELT after stimulation, is termed fibrinolytic potential[14]. The aim of the present study was to assess plasma fibrinolytic activity and fibrinolytic potential in patients with peripheral vascular disease before femoropopliteal bypass surgery. Femoropopliteal graft patency was assessed in the short term after 1 month and subsequently again in the long term to determine whether plasma fibrinolytic activity had any effect on graft patency.

Patients and methods

Fibrinolytic activity was studied in 51 patients: 35 men and 16 women. The mean age of the patients was 69 years; 26 (51 per cent) were current cigarette smokers and 12 (24 per cent) had diabetes mellitus. All patients had peripheral vascular disease, the indication for surgery being claudication or aneurysm in 12 (24 per cent) and ischaemic rest pain in 39 (76 per cent).

Before surgery, all patients had plasma fibrinolytic activity measured at rest, and fibrinolytic potential measured after stimulation by a 10 min venous occlusion test[15]. Patients were tested in the morning after at least 30 min rest in bed to avoid the effects of exercise and the diurnal variation in fibrinolytic activity. A 0·6 mm butterfly cannula was inserted into the largest antecubital fossa vein and a 5 ml venous sample was withdrawn. A sphygmomanometer cuff was placed around the upper arm and inflated midway between systolic and diastolic blood pressure for 10 min. Before the cuff was deflated the cannula was cleared and a second 5 ml venous sample withdrawn. The venous blood samples were placed into citrate and taken immediately to the haematology laboratory where a euglobulin lysis time (ELT) was estimated by the method of Buckell[16].

All the patients had femoropopliteal bypass grafts inserted under general anaesthesia. The material used for bypass was *in situ* vein in 45 (88 per cent) patients and polytetrafluoroethylene (PTFE) in 6 (12 per cent) patients. Graft function was initially assessed after 1 month or at hospital discharge if this was sooner. The patients were followed in the outpatient clinic where graft patency was noted at each visit. The methods used to determine graft patency were clinical examination and Doppler flowmetry. Where there was doubt about graft patency, digital subtraction angiography was performed, often on an outpatient basis.

Fibrinolytic activity and fibrinolytic potential were compared in patients with functioning and those with thrombosed grafts after 1 month and again at the end of the study period. Statistical comparison of the ELTs was performed using the Mann–Whitney *U* test. Other risk factors for graft thrombosis were compared by χ^2 analysis. Stepwise logistic regression analysis (BMPD Statistical Software Inc.) was performed on the known risk factors of graft thrombosis to determine the relative importance of defective fibrinolysis.

Results

Early results

The 51 femoropopliteal grafts were inserted satisfactorily and all the patients survived at least 1 month after surgery. At 1 month, 12 (24 per cent) grafts had thrombosed. The significant risk factors for graft thrombosis were age and the indication for surgery. The mean age of the patients with thrombosed grafts (74 years) was greater than those with functioning grafts (67 years) ($\chi^2 = 7{\cdot}3$, $P = 0{\cdot}007$). All 12 patients with graft thrombosis had surgery for ischaemic rest pain, whereas the grafts inserted for claudication or aneurysm all continued to function ($\chi^2 = 5{\cdot}4$, $P = 0{\cdot}02$). Early graft thrombosis was more frequent in the 11 patients with one vessel run-off or worse (45 per cent), compared with the 38 patients with two or three vessel run-off (18 per cent),

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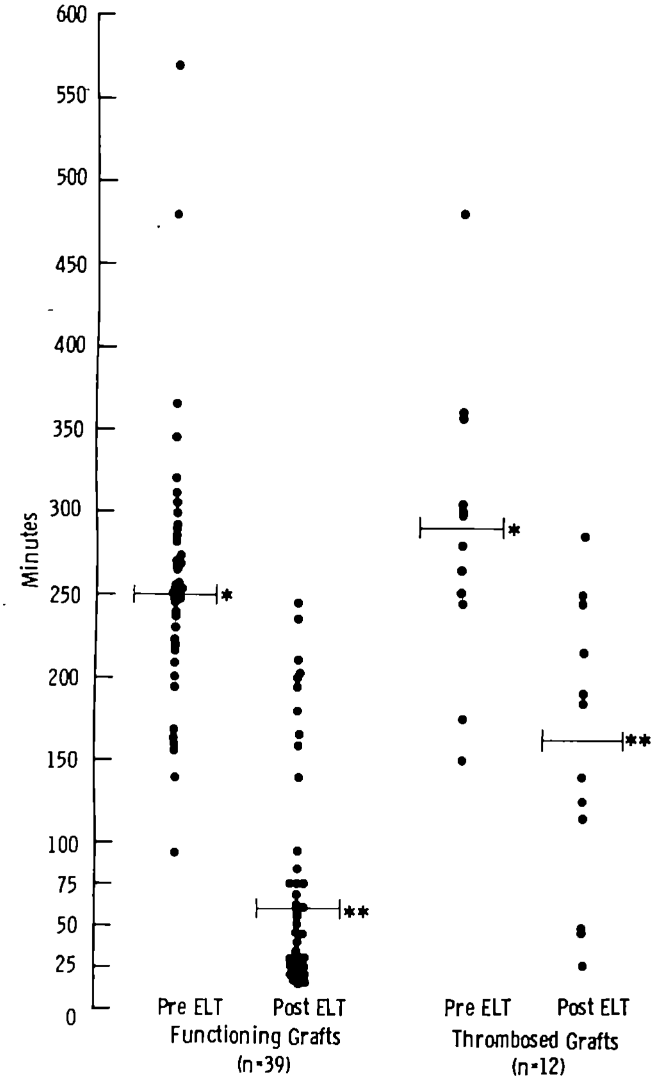

Figure 1 *Resting plasma fibrinolytic activity (pre-ELT) and fibrinolytic potential (post-ELT) 1 month after femoropopliteal reconstruction.* *U=*168*, P=*0·14*, n.s.* **U=*124·5*, P=*0·015*

though this did not achieve statistical significance ($\chi^2=3{\cdot}1$, $P=0{\cdot}07$). There was no added risk associated with diabetes, smoking or the type of graft material used. Nine vein grafts and three PTFE grafts thrombosed.

There was no difference in resting fibrinolytic activity between patients with functioning grafts (median pre-ELT = 250 min) and those with thrombosed grafts (285 min) ($U=168$, $P=0{\cdot}14$) (*Figure 1*). However, there was a difference in fibrinolytic potential which was significantly reduced in patients with graft thrombosis (median post-ELT = 165 min) compared to those with functioning grafts (65 min) ($U=124{\cdot}5$, $P=0{\cdot}015$).

Thus when taken individually the significant risk factors for early graft thrombosis were age, fibrinolytic potential and the indication for surgery. Stepwise logistic regression analysis demonstrated that age ($\chi^2=7{\cdot}3$, $P=0{\cdot}007$), fibrinolytic potential ($\chi^2=6{\cdot}6$, $P=0{\cdot}01$) and indication for surgery ($\chi^2=4{\cdot}6$, $P=0{\cdot}03$) all contributed independently to the prediction of graft thrombosis. All other factors studied failed to reach significance.

Late results

After 1 month 39 patients had functioning grafts. Four patients subsequently died, two after myocardial infarctions, one from a stroke and one from bronchopneumonia. A fifth patient had a PTFE graft removed after 3 months due to graft infection. The remaining 34 patients were followed up for a mean of 9 months. A further eight grafts thrombosed during this period. Graft failure occurred between 6 weeks and 10 months after insertion, though all but one had thrombosed within 5 months.

There were no differences in fibrinolytic activity or fibrinolytic potential in patients with functioning or thrombosed grafts (*Figure 2*). Resting fibrinolytic activity in patients with patent grafts (median pre-ELT = 250 min) was similar to that in patients with graft thrombosis (260 min) ($U=90$, $P=$n.s.). Fibrinolytic potential was also similar in patent grafts (median post-ELT = 50 min) compared with thrombosed grafts (60 min) ($U=94$, $P=$n.s.). There were no differences between the two groups in any of the other risk factors studied for early graft thrombosis, namely age, indication, run-off, graft material, diabetes or smoking.

Discussion

Femoropopliteal bypass graft thrombosis frequently results in amputation, especially if it occurs in the first month after insertion. Platelet deposition has been implicated as the initiator of graft thrombosis because radiolabelled platelets have been shown to accumulate along the length of newly implanted grafts[17], and platelets have been found to have a reduced life span after vascular reconstruction. However, other changes in the coagulation system, including deficiency of anti-thrombin III which is a potent inhibitor of thrombin and Factor Xa, have also been shown to predispose to graft thrombosis[18]. It may be

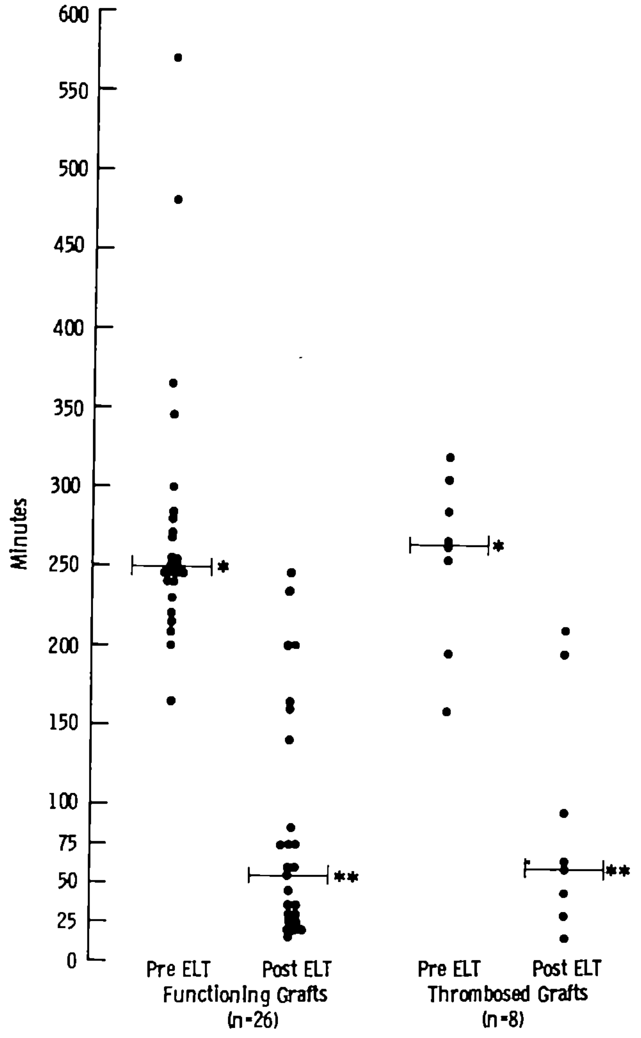

Figure 2 *Resting plasma fibrinolytic activity (pre-ELT) and fibrinolytic potential (post-ELT) after a mean of 9 months in patients whose femoropopliteal grafts were patent 1 month after insertion.* *U=*90*, P=*n.s.* **U=*94*, P=*n.s.*

argued that there is a risk from any form of overactive coagulation. Assuming a balance exists between coagulation and fibrinolysis it is not surprising that defective fibrinolysis can also be shown to be a risk factor for graft thrombosis.

In the present study fibrinolytic potential, though not fibrinolytic activity, was shown to be an independent risk factor for early graft thrombosis. Fibrinolytic potential has been reported to be reduced in patients whose aorto-coronary grafts thrombosed[19], but it has not previously been reported as a risk factor in femoropopliteal graft thrombosis. Local fibrinolytic activity has been shown to be reduced in the walls of femoropopliteal vein grafts which subsequently thrombosed[20].

Though the early graft thrombosis rate (24 per cent) was high, no antithrombotic medication was used and the risk factors identified in this study were similar to those reported by others[21]. The calibre of vein grafts was not measured routinely, but veins below 3 mm in diameter were usually rejected. None of the patients had simultaneous inflow reconstruction, though a few had a peroperative angioplasty if a papaverine test revealed a significant pressure drop. *In situ* vein grafts were checked for technical defects by on-table angiography. There was no preponderance of grafts below the knee in the study, and patency rates were similar for above and below knee femoropopliteal grafts. Despite careful study, no other risk factors known to affect graft patency adversely could be identified[22] and it was concluded that the high graft failure rate was a chance finding in a relatively small series. In this unit the 1-year graft patency has been recorded as 40 per cent for PTFE grafts and 67 per cent for the first 100 *in situ* femoropopliteal vein grafts.

Though the ELT is a non-specific estimate of overall fibrinolytic activity, it has been recommended as a simple test for population studies[23]. The ELT after venous occlusion, unlike the ELT before occlusion, has the advantage that it is independent of the plasma fibrinogen concentration, and therefore the effects on graft patency are not simply explained by plasma viscosity[12]. Plasma fibrinolytic activity represents a balance between plasma plasminogen activator and its specific fast inhibitor (PAI). Defective fibrinolysis may be due to reduced release of plasminogen activator, though recently elevated PAI levels have been shown to be the more important cause in venous thrombosis[3] and ischaemic heart disease[10]. Fibrinolytic shutdown is known to occur after major surgery[24] and may be caused by release of PAI in an acute phase reaction. It is unknown whether this has any relevance to graft thrombosis and further studies on the relative importance of plasminogen activator and PAI levels in thrombosis are required.

Late graft thrombosis is usually stated to be due either to intimal hyperplasia narrowing the graft lumen, or due to progression of distal disease[18]. In the present study the number of patients followed long term was small and it was therefore not surprising that neither defective fibrinolysis nor any of the other risk factors studied were found to affect graft thrombosis.

The pharmacological approach to improved graft patency began with the prevention of coagulation using warfarin. However, although full anticoagulation may improve graft patency in both the short and the long term[25], there is an unacceptable morbidity from bleeding problems. More recently, studies have concentrated on prevention of platelet activation. Aspirin alone and in combination with dipyridamole has been shown to improve patency in small calibre grafts[26]. Other new cyclo-oxygenase inhibitors such as indobufen have had a similar effect in animal studies and may be more acceptable to the patients[27].

A novel approach for prevention of graft thrombosis may be to stimulate the fibrinolytic system. Oxpentifylline has recently been shown to be superior to aspirin with dipyridamole in the prevention of femoropopliteal graft thrombosis[28]. This was accounted for by the effects of the drug on the fibrinolytic system. However, oxpentiphylline has other effects on red cell deformability and plasma viscosity. Another agent which may be suitable for fibrinolytic stimulation is stanozolol, an anabolic steroid which has been shown to enhance fibrinolytic activity in both patients and controls[29,30].

In conclusion, the high rate of graft thrombosis documented in this study cannot be explained by detailed examination of the risk factors and therefore does not invalidate the conclusion that defective fibrinolytic potential was an independent risk factor for early femoropopliteal graft thrombosis. If the results of the present study are confirmed, further trials of fibrinolytic enhancement during femoropopliteal grafting would be worthwhile. It is not inconceivable that the ideal method of prevention of graft thrombosis might be fibrinolytic enhancement with additional platelet inhibition.

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Changes in the apparently normal limb in unilateral venous ulceration

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Forty-seven patients with unilateral venous ulceration have been investigated to determine if any abnormalities were present in the contralateral limbs which had not had lipodermatosclerosis or ulceration. Ascending phlebography in the non-ulcerated limbs showed post-thrombotic changes in 28 per cent and incompetent lower leg communicating veins in 19 per cent. This incidence was not significantly different to the limbs with healed ulceration (45 and 23 per cent respectively, χ^2 *test,* $P=0{\cdot}10$*). Half volume refilling time measured by foot volumetry suggested that 79 per cent of the non-ulcerated limbs had evidence of deep vein incompetence or incompetent lower leg communicating veins, which was again similar to the incidence in the previously ulcerated limbs (85 per cent). Transcutaneous oxygen readings, expressed as a ratio of a reading at a standard site in the gaiter region of the leg over a reading from the upper arm, were significantly lower in non-ulcerated limbs (mean* $0{\cdot}84 \pm 0{\cdot}26$ *s.d.) than in a cohort of age and sex matched controls (mean* $1{\cdot}02 \pm 0{\cdot}14$*, Student's* t *test,* $P<0{\cdot}001$*), and significantly higher than in previously ulcerated limbs (mean* $0{\cdot}68 \pm 0{\cdot}31$*,* $P<0{\cdot}01$*). Abnormalities in venous anatomy and function have been shown, in conjunction with evidence of reduced oxygen diffusion, through the gaiter skin before overt skin changes develop.*

Keywords: Venous ulcer, transcutaneous oxygen tension, calf pump abnormality

The underlying abnormality in limbs with venous ulceration is a defective calf muscle pump[1]. Post-thrombotic changes in the deep veins, incompetence of the lower leg communicating veins, or incompetence of the saphenous veins may all reduce the efficiency of the pump, and produce venous hypertension in the surface veins of the calf and foot during exercise[2,3]. High ambulatory venous pressure has been related to an increase in the size of the dermal capillary bed of the gaiter skin[4], and the 'pre-ulcer' skin changes of lipodermatosclerosis have been shown to contain pericapillary fibrin deposits in the dermis on biopsy[5]. A reduction in the fibrinolytic capacity of patients with lipodermatosclerosis may encourage fibrin deposition and hinder its re-absorption[6]. Pericapillary fibrin deposits have been postulated to act as a diffusion barrier to oxygen and result in hypoxia of the overlying skin[7], which may be a major factor in the development of venous ulceration[7–9].

As there are many causes for leg ulcers, it is imperative to assess the anatomy and function of the leg veins before a confident diagnosis of venous ulceration can be made. A number of investigations are usually performed since no one investigation can establish the diagnosis with certainty in every patient. The anatomy of the deep veins and incompetence of the lower leg communicating veins can be demonstrated by ascending phlebography, while descending phlebography allows an assessment of reflux in the femoral and long saphenous veins[10]. Calf muscle pump function can be assessed by the measurement of foot vein pressures on exercise[2,3], or phlethysmography using strain gauges[11], air[12], water[13] or photo-electric methods[14]. The concept of skin hypoxia has been supported by the demonstration of lower transcutaneous oxygen tensions in lipodermatosclerotic skin[8,15], and the demonstration of lower oxygen consumption in limbs with lipodermatosclerosis and venous ulceration[9].

A venous ulcer represents the end point of the underlying abnormality in these limbs, and is the most difficult stage of this condition to treat. The ideal time to start treating limbs at risk is before skin changes develop. In most instances this ideal cannot be realized because 'at risk' limbs cannot be identified. One occasion where this may be possible is in the apparently 'normal' limb, without lipodermatosclerosis or ulceration, of patients with unilateral venous ulceration. Since deep venous thrombosis is known to occur bilaterally in a substantial percentage of cases[16], and congenital abnormalities of the veins or vein walls are unlikely to affect only one limb[17], it is not unreasonable to expect similar changes in the non-ulcerated limbs to those found in the ulcerated limbs. We have, therefore, studied the non-ulcerated limbs in patients with unilateral venous ulceration, to see if we can detect abnormalities in the leg vein anatomy, calf muscle pump function and cutaneous oxygen diffusion.

Patients and methods

We have assessed 82 patients attending the venous ulcer clinic at St. Thomas' Hospital between August 1984 and August 1986. When patients first presented, a detailed history was taken and the lower limbs were carefully examined. The presence or absence of lipodermatosclerosis and varicose veins was noted. Incompetence of lower leg communicating veins was determined by tourniquet tests and saphenous incompetence was determined by tourniquet tests and directional Doppler testing[18]. A number of investigations were performed to exclude other caues of ulceration. These included a full blood picture, the erythrocyte sedimentation rate, blood urea and electrolytes, liver function tests, blood glucose, Rose Waaler titre, rheumatoid factor latex fixation test, antinuclear antibody, and the arterial Doppler ankle/brachial pressure index of the lower limbs.

When the ulcers had healed, both limbs were examined by ascending phlebography, foot volumetry and transcutaneous oxygen measurements. The ascending phlebography was performed by the technique described by Lea Thomas[19]. Phlebographic changes, taken to represent the post-thrombotic state, were: segments of venous occlusion, absence of visible valves, irregular or reduplicated vein lumina, collateral veins bypassing the occluded segments[19]. Incompetent lower leg communicating veins were also identified on ascending phlebography as dilated valveless channels connecting the deep veins to surface varicosities.

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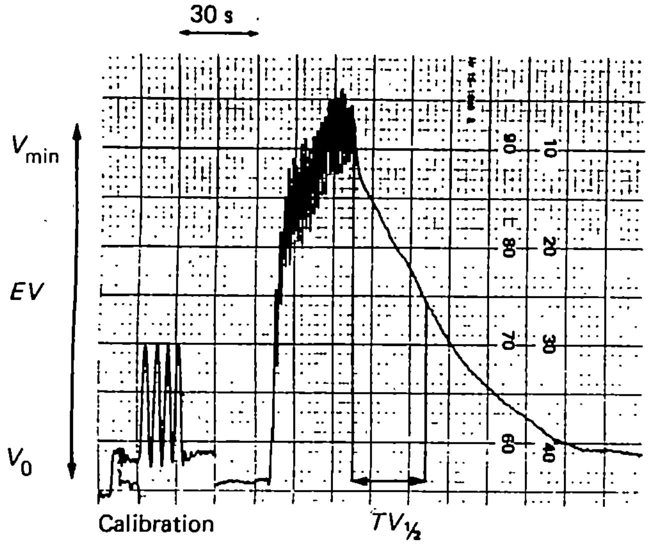

Figure 1 *Foot volumetry tracing from a normal leg, demonstrating the calculations made to obtain the expelled volume* (EV), *the relative expelled volume* (EV_{rel}) *and the half volume refilling time* ($TV_{\frac{1}{2}}$). V_0, *Resting baseline;* V_{min}, *foot volume after exercise; calibration, 10 ml. Our normal ranges are* $EV_{rel}=1{\cdot}5\pm0{\cdot}5$ *ml/100 ml;* $TV_{\frac{1}{2}}=25\pm10$ *s*

Foot volumetry was performed by a modification of the technique described by Norgren[13]. The investigation was repeated with the application of inflatable tourniquets placed above the knee and below the knee to identify long and short saphenous incompetence. The following measurements were made from the tracings: half volume refilling time ($TV_{\frac{1}{2}}$, a measure of venous reflux); and expelled volume (EV, a measure of the pumping function of the calf muscle) (*Figure 1*). In order to allow for the differences in foot sizes, the expelled volume was divided by the resting foot volume to obtain the relative expelled volume (EV_{rel}). A normal range for these measurements has previously been established in our department.

Transcutaneous oxygen tensions (P_{tc,O_2}) were measured by a radiometer transcutaneous oxygen monitor (Radiometer Copenhagen TCM2) with the electrode heated to 45°C. Measurements were performed on both legs at a standard site, 7·5 cm above the medial malleollus, with the patient lying supine. P_{tc,O_2} was also measured on the anterior aspect of the upper arm at the same time and this acted as a control site. We have expressed our results as a ratio of the reading from the leg over the reading from the arm, since it has been shown that expressing the results as a ratio reduces the variability of direct measurements at a single site[20].

Results

Out of 82 patients admitted to the study, 47 patients had evidence of unilateral venous ulceration with no evidence of lipodermatosclerosis and no history of ulceration in the contralateral limb. Thirteen patients had evidence of lipodermatosclerosis in the contralateral limb, but no history of ulceration. A total of 22 patients had had bilateral venous ulceration.

In the 22 patients with bilateral ulceration, 13 patients were able to clearly identify a difference in the time of onset of ulceration in each leg (range 1–40 years, median 9 years). Only one patient could recall the ulceration beginning at the same time in both legs. The remaining eight patients had had ulceration in both legs for more than 10 years and were unable to clearly recall when the ulceration developed. In the patients with unilateral venous ulceration, the time of onset of ulceration ranged from 1 to 30 years with a median time of 4 years.

The results of the clinical examination, phlebography, foot volumetry and transcutaneous oxygen measurements in the 47 non-ulcerated limbs of patients with unilateral venous ulceration are reported here and compared with the findings in the 47 contralateral limbs with healed ulcers. There were 23 men and 24 women with ages ranging from 23 to 84 years with a mean of 58·7 years.

Clinical examination

Of the non-ulcerated limbs 21 showed no evidence of varicose veins or lipodermatosclerosis on examination. Eleven limbs had evidence of isolated long or short saphenous incompetence or both, without any clinical evidence of incompetent lower leg communicating veins. Twelve limbs had evidence of incompetent communicating veins in the lower leg in addition to long or short saphenous incompetence, and three limbs had isolated incompetence of the lower leg communicating veins without any evidence of saphenous incompetence.

The number of limbs with no clinical evidence of venous incompetence and limbs with incompetent lower leg communicating veins were significantly different in the non-ulcerated compared with the previously ulcerated limbs (χ^2 test, $P<0{\cdot}01$, *Figure 2*).

Ascending phlebography

In 25 of the non-ulcerated limbs there were normal deep veins without evidence of incompetent lower leg communicating veins. Thirteen limbs had post-thrombotic changes in the deep veins of the leg. Nine limbs had incompetent lower leg communicating veins without evidence of post-thrombotic changes.

The distribution of the phlebographic findings in the non-ulcerated limbs was not significantly different from the previously ulcerated limbs (χ^2 test, $P=0{\cdot}10$, *Figure 3*).

Foot volumetry

Only four of the non-ulcerated limbs had a normal ($TV_{\frac{1}{2}}$). Four limbs had pure long saphenous vein incompetence confirmed by a return to normal of the $TV_{\frac{1}{2}}$ by the application of an above knee tourniquet. Two limbs had pure short saphenous vein incompetence confirmed by a return to normal of the $TV_{\frac{1}{2}}$ when a below knee tourniquet was applied. A total of 37 limbs had evidence of deep vein incompetence or incompetence of the lower leg communicating veins since the $TV_{\frac{1}{2}}$ could not be returned to normal by the application of tourniquets.

The distribution of these findings in the non-ulcerated limbs

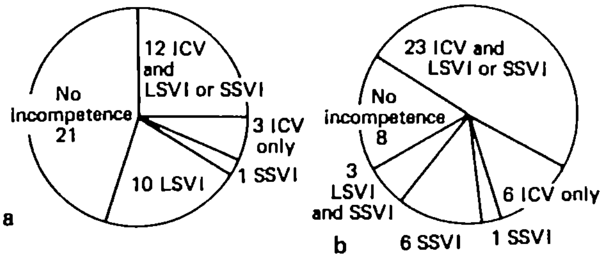

Figure 2 *Results of clinical examination.* **a**, *Contralateral 'normal' limbs;* **b**, *previously ulcerated limbs; ICV, incompetent lower leg communicating veins; LSVI, long saphenous vein incompetence; SSVI, short saphenous vein incompetence*

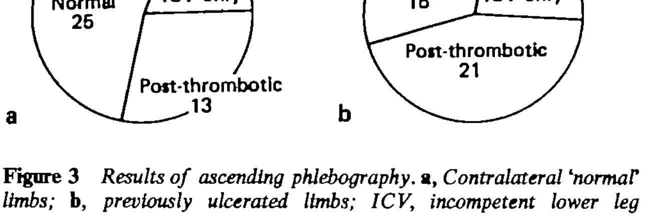

Figure 3 *Results of ascending phlebography.* **a**, *Contralateral 'normal' limbs;* **b**, *previously ulcerated limbs; ICV, incompetent lower leg communicating veins*

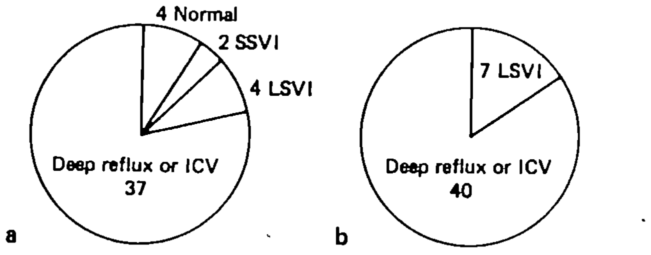

Figure 4 *Results of half volume refilling time on foot volumetry.* **a**, *Contralateral 'normal' limbs;* **b**, *previously ulcerated limbs; ICV, incompetent lower leg communicating veins; LSVI, long saphenous vein incompetence; SSVI, short saphenous vein incompetence*

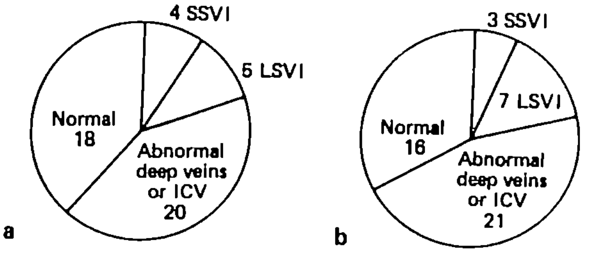

Figure 5 *Results of relative expelled volume on foot volumetry.* **a**, *Contralateral 'normal' limbs;* **b**, *previously ulcerated limbs; ICV, incompetent lower leg communicating veins; LSVI, long saphenous vein incompetence; SSVI, short saphenous vein incompetence*

was not significantly different from the previously ulcerated limbs (χ^2 test, $P > 0\cdot10$, *Figure 4*).

The relative expelled volume (EV_{rel}) was also calculated and compared for these limbs. Of the non-ulcerated limbs, 18 had a normal EV_{rel}. Five limbs had pure long saphenous vein incompetence, four limbs had pure short saphenous vein incompetence and twenty limbs had evidence of deep vein incompetence or incompetence of the lower leg communicating veins.

The distribution of these findings in the non-ulcerated limbs was not significantly different to the previously ulcerated limbs (χ^2 test, $P > 0\cdot50$, *Figure 5*).

Transcutaneous oxygen tensions

The readings in the non-ulcerated limbs have been compared with those in the previously ulcerated limbs, and with control readings taken from a group of age and sex matched patients with no history of deep venous thrombosis or venous ulceration, and no signs of ischaemic arterial disease. The mean transcutaneous oxygen arm to leg ratio for the control limbs was $1\cdot02 \pm 0\cdot14$ (s.d.), for the contralateral non-ulcerated limbs it was $0\cdot84 \pm 0\cdot26$, and for the previously ulcerated limbs it was $0\cdot68 \pm 0\cdot31$. The P_{tc,O_2} ratios in the non-ulcerated limbs were significantly greater than ratios from the previously ulcerated limbs (Student's t test, $P < 0\cdot01$), but were significantly lower than those for the control limbs ($P < 0\cdot001$, *Figure 6*).

Results in limbs without clinical venous incompetence or lipodermatosclerosis

If the non-ulcerated limbs without clinical venous incompetence are considered separately, the findings on foot volumetry and phlebography are similar to those in the non-ulcerated limbs with clinical venous incompetence (*Table 1*). The mean transcutaneous oxygen ratio for these 'normal' limbs is $0\cdot78 \pm 0\cdot22$ compared with a mean of $0\cdot88 \pm 0\cdot28$ for the limbs with clinical evidence of venous incompetence. This is not significantly different statistically, $P = 0\cdot19$.

Discussion

The lower limbs of each patient in this study appear quite different on simple inspection. One limb has previously had a venous ulcer which has healed. Of these 47 limbs, 44 had evidence of lipodermatosclerosis. The contralateral limbs have no history of ulceration and no evidence of lipodermatosclerosis. Clinical examination for venous incompetence demonstrated significant differences between these two groups of limbs. The oxygen diffusion through the skin of the limbs was significantly higher in the contralateral non-ulcerated limbs compared with the previously ulcerated limbs. However, this was still significantly lower than in a group of healthy controls.

In contrast, the findings on ascending phlebography and foot volumetry in the two groups of limbs were not significantly different. Of the contralateral non-ulcerated limbs, 47 per cent had abnormal deep veins or incompetent lower leg communicating veins on ascending phlebography, and 79 per cent had evidence of deep vein incompetence or incompetent lower leg communicating veins on foot volumetry.

The contralateral non-ulcerated limbs with clinical evidence of venous incompetence, and those without, were considered separately. The abnormalities found on ascending phlebography and foot volumetry, as well as the transcutaneous oxygen ratios, were similar in both of these subgroups of limbs.

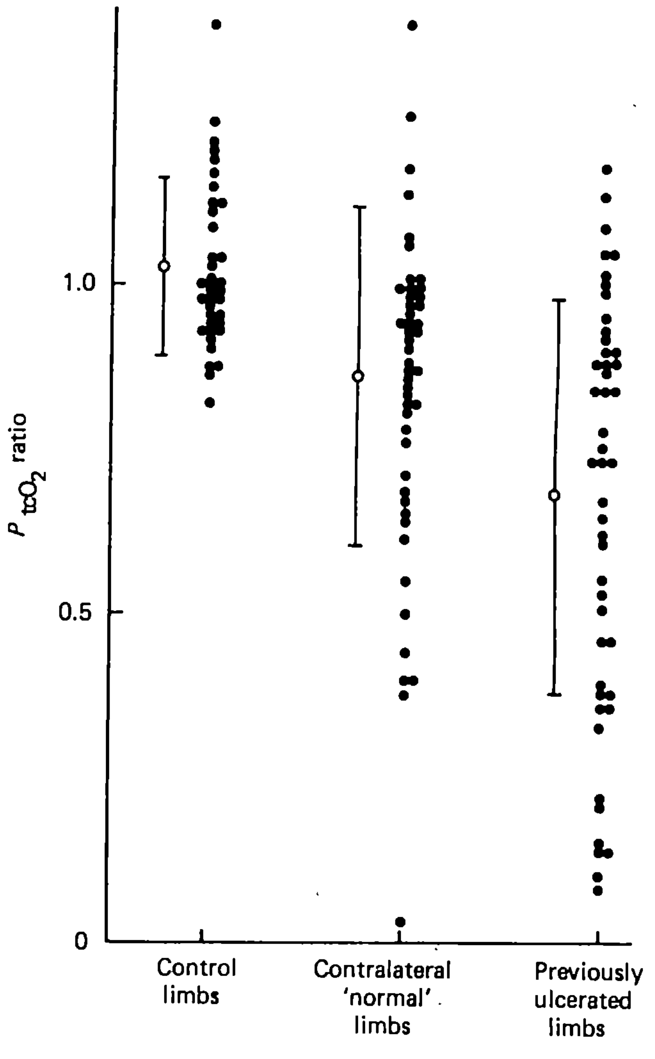

Figure 6 *Transcutaneous oxygen ratios for the control limbs, the contralateral non-ulcerated limbs and the previously ulcerated limbs in patients with a healed unilateral venous ulcer. The ratios for the contralateral non-ulcerated limbs are significantly lower than those for the control limbs* (P<0·001, *Student's* t *test*), *and significantly greater than those for the previously ulcerated limbs* (P<0·01, *Student's* t *test*). ⊢○⊣, *mean* ± *1 s.d.*

Table 1 *Distribution of findings of ascending phlebography and foot volumetry in the contralateral non-ulcerated limbs with normal skin, separated into those limbs with clinical evidence of venous incompetence and those without*

	No clinical venous incompetence	Clinical venous incompetence
Ascending phlebography		
Normal	9 (43)	16 (62)
ICV	5 (24)	4 (15)
Post-thrombotic	7 (33)	6 (23)
Foot volumetry ($TV_{\frac{1}{2}}$)		
Normal	4 (19)	0 (0)
LSVI	2 (9)	2 (8)
SSVI	2 (9)	0 (0)
Abnormal	13 (62)	24 (92)
Foot volumetry (EV_{rel})		
Normal	6 (28)	12 (46)
LSVI	4 (19)	1 (4)
SSVI	1 (5)	3 (12)
Abnormal	10 (48)	10 (38)

Numbers in parentheses are percentages. ICV, incompetent lower leg communicating veins; LSVI, long saphenous vein incompetence; SSVI, short saphenous vein incompetence; $TV_{\frac{1}{2}}$, half volume refilling time; EV_{rel}, relative expelled volume

This implies that the clinical assessment for venous incompetence in these contralateral non-ulcerated limbs is not accurate in detecting the underlying abnormalities in the deep veins or lower leg communicating veins.

The findings of this study suggest that the underlying cause, whether it is deep venous thrombosis or a congenital abnormality of the vein wall or valves, affects both legs. However, the extent of this abnormality and the time taken for skin changes to develop would appear to be variable. This is supported by the finding that 13 of the 35 patients with bilateral skin changes had unilateral ulceration while lipodermatosclerosis, the presumed precursor of venous ulceration, was present in the other leg. In the 22 patients with bilateral ulceration, the median difference in the time of onset of venous ulceration was 9 years, whereas the median time of onset of ulceration in patients with unilateral ulceration was 4 years. This suggests that, in time, those contralateral non-ulcerated limbs with underlying abnormalities may go on to develop the skin changes of lipodermatosclerosis and venous ulceration.

This study has not aimed to compare the different methods of investigation of limbs with previous venous ulceration. Any comparison of these investigations from this study should be considered carefully. One point of interest was that there was no correlation between the transcutaneous oxygen ratios and either the $TV_{\frac{1}{2}}$ or EV_{rel} (correlation coefficients 0·02 and 0·21, respectively). Similarly, there was no significant difference in the transcutaneous oxygen ratios for limbs with post-thrombotic change, incompetent lower leg communicating veins or limbs normal on phlebography (means 0·87, 0·80 and 0·84, respectively). There may be two explanations for this. First, other factors such as impairment of local fibrinolytic activity may play a more important role in determining skin hypoxia. Secondly, the time taken for skin hypoxia to develop in the presence of an abnormality of the calf muscle pump may vary.

The demonstration of significantly lower transcutaneous oxygen ratios in the apparently 'normal' limbs compared with healthy control limbs, suggests that an oxygen diffusion barrier, and hence pericapillary fibrin deposits in the dermis, have already developed before overt skin changes are apparent.

This study shows that the apparently 'normal' contralateral limb in unilateral venous ulceration is abnormal in a significant proportion of cases. Similar changes are found in both limbs on many occasions, indicating that the contralateral limb should also be carefully assessed when a unilateral venous ulcer has healed. These limbs should not be used as 'controls' in studies of ulcerated limbs. Graduated compression elastic stockings may prevent the future development of overt skin changes and ulceration in these 'high risk' limbs.

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Preservation of the entire anal canal in conservative proctocolectomy for ulcerative colitis: a pilot study comparing end-to-end ileo-anal anastomosis without mucosal resection with mucosal proctectomy and endo-anal anastomosis

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Mucosal proctectomy with endo-anal pull-through anastomosis (MP + PTA) for ulcerative colitis reduces resting anal pressure and low RAP has been found to correlate with minor leakage of faeces or mucus. Our hypothesis was that conservative proctocolectomy with an end-to-end ileo-anal anastomosis (EEA) would result in higher anal pressure and less leakage. Twelve patients were studied after EEA and 24 after MP + PTA: each was in good health several months after operation. After EEA, maximal RAP decreased from a median 90 cmH_2O (60–116 cmH_2O) to 70 cmH_2O (25–104 cmH_2O, $P<0{\cdot}01$), whereas after MP + PTA maximal RAP decreased from 85 cmH_2O (70–125 cmH_2O) to 40 cmH_2O (22–80 cmH_2O, $P<0{\cdot}003$). RAP after EEA was significantly greater than RAP after MP + PTA ($P<0{\cdot}001$). The pressure profile of the anal sphincter in the EEA group did not differ significantly from that of the pre-operative group at any point from 6 to 1 cm from the anal verge, and the sphincteric high pressure zone averaged 4 cm in length both before and after operation. After MP + PTA, resting anal pressure at stations 1 to 4 cm from the anal verge was significantly less than pre-operative pressure ($P<0{\cdot}001$) and the sphincteric high pressure zone was only 3 cm in length compared with 4 cm before operation. Anal squeeze pressures were similar in the two groups of patients. After EEA 11 of 12 patients achieved perfect continence, day and night, whereas after MP + PTA 58 per cent of patients experienced minor faecal leakage ($P<0{\cdot}01$). These findings suggest that the entire anal canal should be kept intact in the course of conservative proctocolectomy for ulcerative colitis.

Keywords: Ulcerative colitis, conservative proctocolectomy, mucosal proctocolectomy, ileo-anal anastomosis, resting anal pressure, continence

Mucosal proctectomy with ileo-anal anastomosis and the formation of a pelvic ileal reservoir has largely replaced anoproctocolectomy and ileostomy in the treatment of children and young adults with ulcerative colitis in specialist centres. Such 'sphincter-saving' surgery has undoubtedly improved the quality of life for many patients; however, for some the clinical outcome remains far from perfect, because of symptoms such as frequency or urgency of defaecation, difficulty in evacuating the reservoir, and seepage of mucus or faeces on to the perianal skin. These imperfections of function are attributable in part to the inherent problems of an artificial reservoir and in part to impaired function of the anal sphincter.

Mucosal proctectomy with a pull-through anastomosis (MP + PTA) does not completely 'preserve the anal sphincter', as is often assumed, because much of the anal mucosa is removed and full-thickness ileum is pulled through the denuded sphincter, to be sutured at or close to the dentate line. A significant decrease in resting anal pressure results, and it has been shown that subsequent minor leakage of mucus or faeces can be correlated with this decrease in resting anal pressure[1,2].

Our hypothesis is that resting anal pressure will be closer to normal, and that fewer patients will experience leakage, if the entire anal canal is left intact, without mucosal stripping. The ileo-anal anastomosis is constructed at the top of the anal canal, rather than inside it.

Patients and methods

Patients

Thirty-six patients (20 men and 16 women) were studied. They had undergone conservative proctocolectomy for ulcerative colitis between January 1983 and November 1986. Their median age was 34 years (range 16–57 years). Twelve patients underwent end-to-end ileo-anal anastomosis (EEA, *Figure 1*), without mucosal stripping, and 24 had a standard mucosal proctectomy with pull-through ileo-anal anastomosis (MP + PTA, *Figure 2*) which was constructed a few millimetres above the dentate line (*Table 1*). None of the anastomoses was stenosed at the time of the study. A pelvic ileal reservoir was fashioned in 30 patients (triplicated in 20, duplicated in 8 and lateral ileal in 2); in the remaining 6 patients, ileo-anal anastomosis was performed without a pelvic reservoir (3 EEA and 3 MP + PTA).

Anal sphincteric function

Each patient underwent studies of anal sphincter function at least 3 months after operation. In 12 patients from the MP + PTA group and all patients in the EEA group these measurements were also made before operation. In each patient, the quality of anal continence was assessed by careful questioning about any leakage, anal soreness and the ability to defer defaecation and to discriminate between faeces and flatus. Anal pressure was measured as described previously[1]. Resting anal pressure (RAP) was measured at 1 cm intervals along the anal canal by means of a 5 mm diameter water-filled balloon. The pressure at each station was measured for at least one minute, or until the recording became stable. Pressure in the system was transmitted via a transducer and amplifier (3552 Ormed Ltd, Welwyn Garden City, England) to a chart recorder (5041 Ormed Ltd). Resting anal pressure (RAP) was defined as the maximum pressure recorded in the anal canal during the station pull-through. A second pull-through was performed to measure the rise in anal pressure over basal (maximum squeeze pressure, MSP) on voluntary contraction of the anal sphincter.

Operative technique

We have described previously the technique used in the performance of mucosal proctectomy with pull-through ileo-anal anastomosis[1,3–5]. The earlier papers[1,3,4] detailed a rather tedious technique involving preservation of a long rectal muscular cuff, which necessitated prolonged retraction on the anal sphincter, but for the past 3–4 years, in common with most other authors, we have left only a short, 1–2 cm cuff above the anal canal, which has simplified the procedure and greatly reduced the duration of retraction. The ileo-anal anastomosis was constructed 5–10 mm above the dentate line: ileum was pulled down through the anal canal and all layers of the ileal wall were sutured endo-anally to the anal mucosa and internal sphincter muscle with interrupted Dexon (Davis and Geck, UK) sutures (*Figure 2*).

End-to-end ileo-anal anastomosis (*Figure 1*) involved a similar close perimuscular dissection of the rectum down to the pelvic floor; no anal retraction was required. By means of a linear stapling instrument, the rectum was transected at the anorectal junction (TA30; Autosuture UK Ltd, Ascot, UK) the level of transection being determined both by proctoscopy and by a finger passed into the anus. Strong upward traction on the rectum at this stage permitted transection at a sufficiently low level, as Heald and Allen have noted previously[6]. The end-to-end anastomosis was made by means of a circular stapling device (EEA; Autosuture UK Ltd, Ascot, UK), the spindle of which was passed through the closed proximal end of the anal canal before the head was attached. The ileum was then secured over the head of the instrument with a pursestring and the bowel ends approximated. The gun was 'fired', the 'doughnuts' inspected, and the integrity of the anastomosis tested digitally and by instillation of water. In each patient, the ileo-anal anastomosis was protected by means of a defunctioning ileostomy, which was closed 8–12 weeks later.

Statistical analysis

All grouped data were expressed as median and range. The groups were compared by means of the Wilcoxon matched-pairs signed-rank test for paired data, the Mann–Whitney *U* test for unpaired data and the χ^2 test[7].

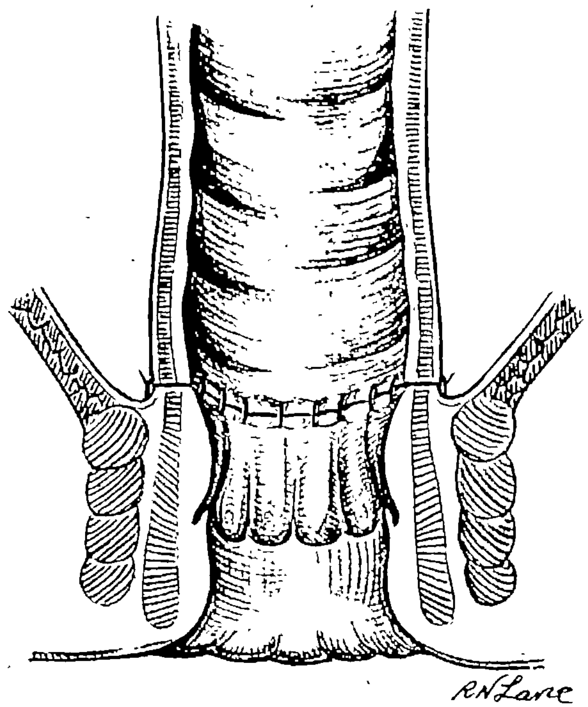

Figure 1 *End-to-end ileo-anal anastomosis (EEA) leaving anal canal completely intact*

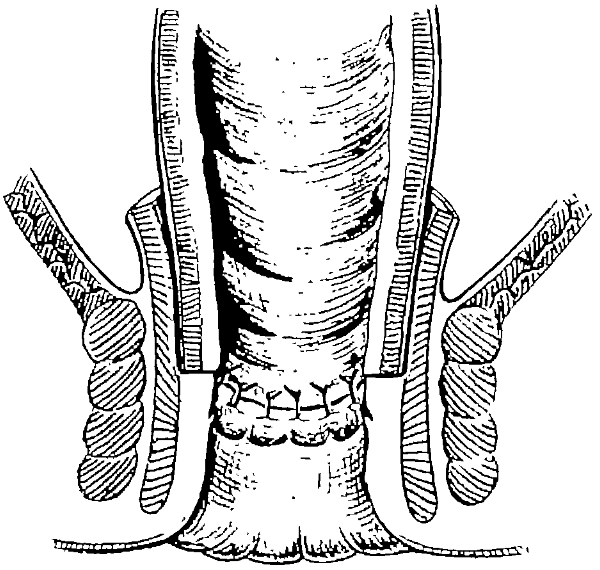

Figure 2 *Mucosal proctectomy with pull-through anastomosis (MP+PTA) just above the dentate line*

Table 1 *Details of the 36 patients who underwent ileo-anal anastomosis and results of anal pressure measurements*

Type of anastomosis	Number	Male:Female	Age median (range) (years)	RAP median (range) (cmH$_2$O)	MSP median (range) (cmH$_2$O)
EEA pre-op.	12	4: 8	37 (18–57)	90 (60–116) *	128 (17–230) *
MP + PTA pre-op.	12	8: 4	30 (20–57)	85 (70–125)	134 (70–210)
Total pre-op.	24	12:12	—	—	—
EEA postop.	12	4: 8	37 (18–57)	70 (25–104) †	146 (39–254) *
MP + PTA postop.	24	16: 8	31 (16–57)	40 (22–80)	137 (38–230)
Total postop.	36	20:16	—	—	—

EEA, End-to-end anastomosis; MP + PTA, mucosal proctectomy with pull-through anastomosis; RAP, maximum resting anal pressure; MSP, maximum squeeze pressure

* Not significant, † $P < 0.001$

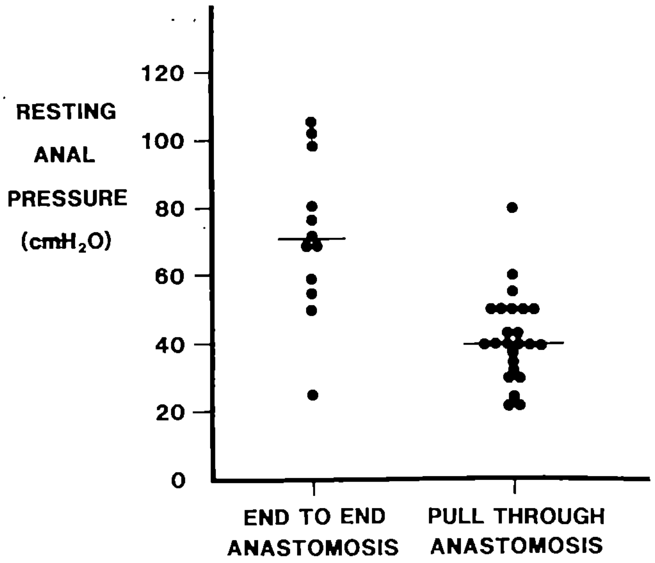

Figure 3 *Maximal resting anal pressure (RAP) was significantly ($P<0{\cdot}001$) greater after end-to-end ileo-anal anastomosis than after mucosal proctectomy with pull-through anastomosis*

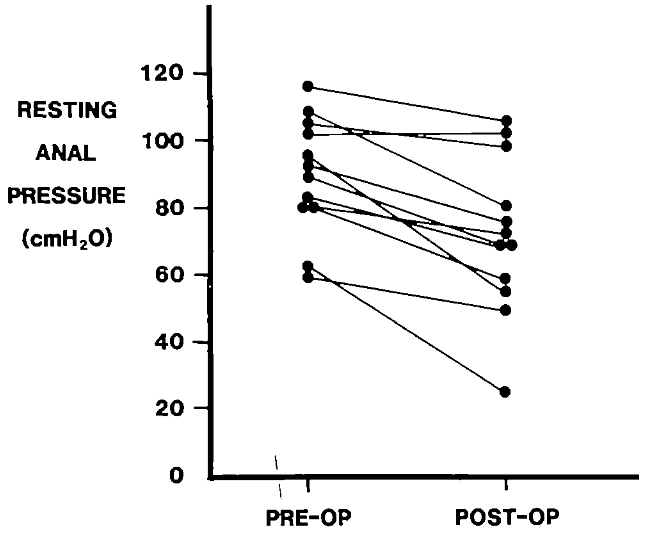

Figure 4 *Maximal resting anal pressure (RAP) decreased significantly ($P<0{\cdot}01$) after end-to-end ileo-anal anastomosis without mucosal stripping (paired tests in the same 12 patients before and more than 3 months after operation)*

Results

Resting anal pressure (RAP)

Before operation, median RAP was 90 cmH_2O (60–116 cmH_2O) in the EEA group and 85 cmH_2O (70–125 cmH_2O) in the MP+PTA group (n.s.).

After operation, median RAP was significantly greater in the EEA group (70 cmH_2O) than in the MP+PTA group (40 cmH_2O, $P<0{\cdot}001$, *Table 1*, *Figure 3*). In both the EEA and the MP+PTA groups, RAP after operation was significantly less than RAP before operation ($P<0{\cdot}01$; *Figure 4* and $P<0{\cdot}003$; *Figure 5*, respectively: *Table 1*).

Profile of resting anal sphincter pressure

Before operation, the site of maximal RAP was in the lower 1 or 2 cm of the anal canal in 90 per cent of patients and the sphincteric high-pressure zone began 4 cm from the anal verge (*Figures 6* and *7*). Thus the length of the anal sphincter before operation averaged 4 cm.

After operation, in the EEA group, RAP did not differ significantly from RAP in the pre-operative patients at any of the recording sites from 6 to 1 cm from the anal verge, and the length of the high-pressure zone remained 4 cm, as in the pre-operative patients (*Figure 6*).

After operation in the MP+PTA group, median RAP was significantly lower than in the pre-operative patients at sites 1, 2, 3 and 4 cm from the anal verge ($P<0{\cdot}0001$, $P<0{\cdot}0001$, $P<0{\cdot}0001$ and $P<0{\cdot}003$ respectively; *Figure 7*), and the mean

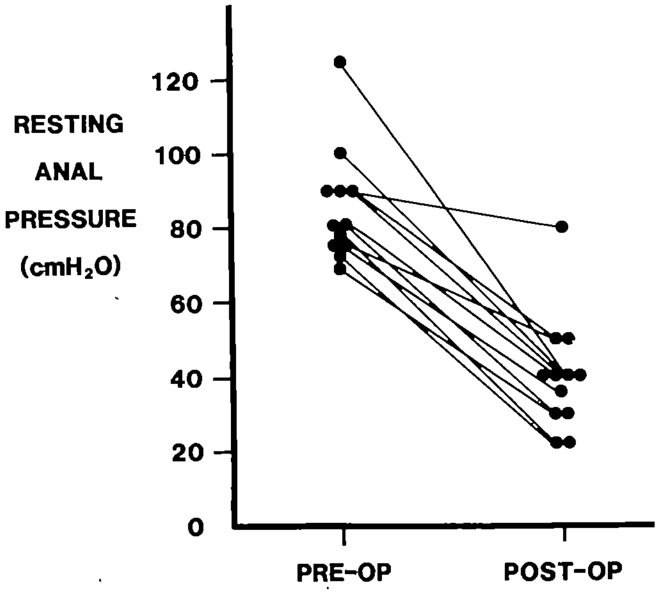

Figure 5 *Maximal resting anal pressure (RAP) decreased significantly ($P<0{\cdot}003$) after mucosal proctectomy and pull-through anastomosis (paired tests in the same 12 patients before and more than 3 months after operation). The decrease in RAP after this procedure is much greater than after end-to-end anastomosis, suggesting impaired function of the internal anal sphincter*

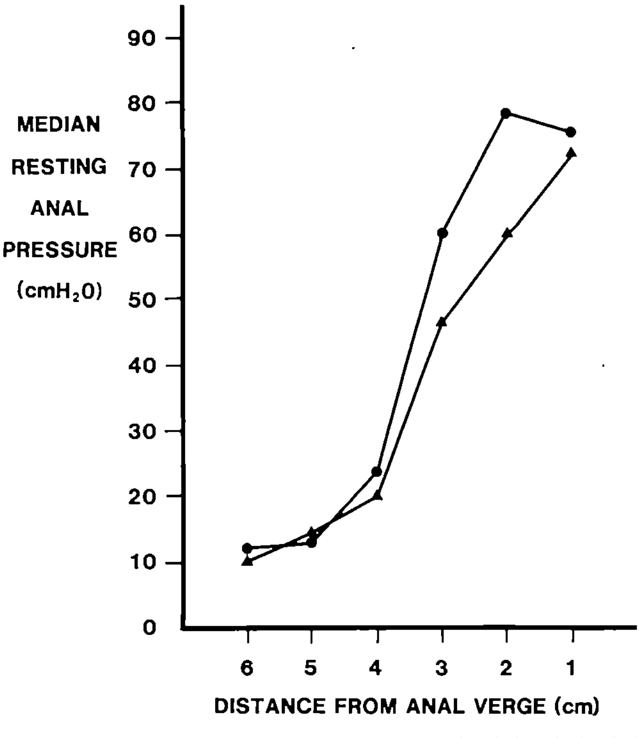

Figure 6 *Pressure profiles of the anal sphincter before (●) and after (▲) end-to-end ileo-anal anastomosis. The length of the high-pressure zone is the same as before operation (4 cm) and the pressure is not significantly different at any point, P = n.s.*

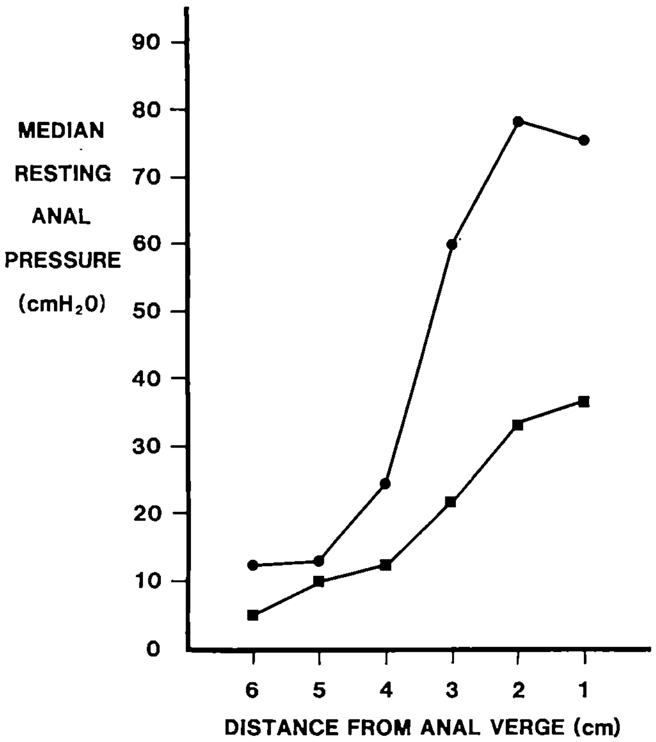

Figure 7 *Pressure profiles of the anal sphincter before (●) and after (■) mucosal proctectomy with pull-through anastomosis (MP+PTA). The anal high-pressure zone is shorter (3 cm) after MP+PTA than before operation (4 cm), and resting anal pressure is significantly* ($P<0.01$) *lower from 4 cm to 1 cm from the anal verge, suggesting that the function of the internal anal sphincter is impaired*

length of the sphincteric high-pressure zone was 3 cm, 1 cm less than in the EEA group and the pre-operative patients.

Maximal squeeze pressure (MSP) did not differ significantly between the EEA group and the MP + PTA group, either before or after operation (*Table 1*).

Minor faecal leakage

Eleven of 12 patients with end-to-end ileo-anal anastomosis were completely continent, without any leakage of faeces or mucus. In contrast, 14 of the 24 patients (58 per cent) who had undergone mucosal proctectomy with pull-through anastomosis reported some leakage of faecal fluid or mucus from the anal canal, although the amount was usually small (EAA *versus* MP+PTA, $\chi^2=8.22$, $P<0.01$). None of the patients experienced major leakage or incontinence, and none required intubation of the pouch.

Discussion

The principal findings were that after end-to-end ileo-anal anastomosis (EEA), without mucosal stripping, both resting anal pressure (RAP) and the pressure profile of the anal sphincter were much closer to normal than were RAP and the sphincteric pressure profile after mucosal proctectomy with pull-through anastomosis (MP+PTA). After MP+PTA, the mean length of the anal high-pressure zone decreased from 4 to 3 cm, whereas after EEA it remained unchanged. Anal pressures in the patients before operation were similar to those of normal people.

These results are in agreement with previous reports from this Department[1–4] that resting anal pressure (RAP) decreases by about 50 per cent after mucosal proctectomy with PTA, and that such a decrease in RAP is not transient, but lasts for 3 months (as in this study) to 13 months[4], and so is presumably permanent. This decrease in RAP is of great clinical importance, because, as our own and other studies have shown previously[1,2], it causes, or more precisely shows a significant correlation with, defects of continence, such as minor seepage or leakage of mucus or faeces from the anus. The findings in this study lend further support to this idea, because among the 12 patients who underwent EEA, only one experienced any leakage or perianal soreness, whereas no fewer than 14 of the 24 patients (58 per cent) who underwent MP+PTA experienced leakage, which was often accompanied by perianal itch or soreness. The median duration of follow-up was shorter after EEA than after MP+PTA, which makes the superior clinical results of EEA all the more significant, because frequency and urgency of defaecation and nocturnal incontinence all tend to be worst in the early postoperative months and to improve with time. None of the patients in either group experienced major leakage of faeces or incontinence, but several in the MP+PTA group preferred to wear a pad inside their underclothes.

It has been suggested that the decrease in RAP and the relatively high incidence of minor faecal leakage that we have found after mucosal proctectomy with endo-anal anastomosis are related to the particular operative technique that we used, and may not be applicable to the procedure as it is used in other centres. In particular, the prolonged and vigorous retraction on the anal sphincter that was required, in some patients, to permit the removal of a cylinder of anorectal mucosa and the construction of an ileo-anal anastomosis just above the dentate line, as detailed in our earlier papers[3,4], seemed to provide a plausible explanation for the decrease in RAP and the leakage, and has been criticized as being unnecessary and avoidable. Against this, it must be pointed out that in recent years we have greatly reduced operating time and the duration of anal retraction by leaving only a short cuff of rectal muscle in the course of the mucosal resection, yet the decrease in resting anal pressure remains as great as ever. If stretching of the anal sphincter at operation were the sole explanation of the decrease in RAP, some recovery of function and increase in pressure would be expected with the passage of time, yet in fact we found no significant increase in RAP between 3 and 13 months after MP+PTA, in paired tests in 13 patients[4]. Sir Alan Parks was sceptical of the idea that anal dilatation damaged the anal sphincter: 'this is not true in practice, and consideration of the fact that the most important sphincter, that is, the puborectalis, is stretched to the diameter of a child's head during childbirth should be testimony enough of the plastic resilience of the anal sphincters'[8].

The literature on the effects of mucosal proctectomy with endoanal ileo-anal anastomosis on the function of the anal sphincter and continence is extensive, and still increasing rapidly. It is thus not surprising that reports should vary[1–6,9,10], and that some centres should claim near-perfect results after MP+PTA: operative techniques vary, techniques of anorectal manometry differ, and some authors are more critical of their results than others. Nevertheless, it must be borne in mind that at the Mayo Clinic, where more than 650 MP+PTA procedures with a duplicated J pouch have now been performed, K. A. Kelly and his colleagues have found that approximately 50 per cent of patients experience some nocturnal leakage during the first postoperative year, and that resting anal pressure decreases significantly, albeit to a lesser extent than we have found[11]. Similarly, at St. Mark's Hospital, where Nicholls and his colleagues conducted a detailed pathophysiological study[2] of 14 patients after MP+PTA (with a triplicated pouch), 50 per cent of the patients experienced some leakage of mucus and had low anal pressures (37 ± 9 cmH_2O), while the remainder had no leakage, and normal anal pressures (79 ± 19 cmH_2O).

Naturally, not all the symptoms that are experienced by patients after conservative proctocolectomy can be attributed to impaired function of the anal sphincter. Other factors are involved, such as high stool volume, impaired emptying or inflammation of the ileal reservoir, and high-pressure contractions in the reservoir. We also do not wish to imply that all patients with a low RAP or minor leakage after MP+PTA have a poor clinical result: many of them are in fact quite pleased with the result, and cheerfully put up with minor imperfections of anal function in return for their restoration to good health and the absence of an ileostomy. None the less, the results of this and of our previous studies, and those from other centres, leave us in no doubt that mucosal proctectomy with an endoanal anastomosis impairs both the sensory and the motor functions of the anal sphincter, and is followed by minor leakage in many patients. Retraction on the anal sphincter is probably not a major cause of these defects, which are more probably attributable to interruption of Meissner's intramural nerve plexus, upon which the dynamic properties of the internal anal sphincter largely depend[12], removal of the mucosa from the sampling zone in the upper canal[13,14], and the physical presence of full-thickness ileum within the anal canal.

In contrast with the evidence of impaired function of the internal anal sphincter after MP+PTA, no impairment of function of the external anal sphincter was found, either after EEA or after MP+PTA, as shown by the finding of normal maximal squeeze pressures.

This was a pilot study, to test a hypothesis. The results obtained were encouraging, as they tended to confirm both our ideas about the value of preserving the whole anal canal and our previous findings with regard to the pull-through procedure. Nevertheless, the numbers of patients tested were relatively small, the duration of follow-up in the two groups of patients was unequal, and so the findings require confirmation, preferably by a prospective trial.

As far as we are aware, preservation of the entire anal canal in the manner that we have described has not been advocated previously for use in patients with ulcerative colitis. Heald and Allen[6] described excellent clinical results after the use of the stapling gun to construct an ileo-anal anastomosis, but in their patients the anastomosis was constructed at, or very close to, the dentate line, whereas in the patients in this study, the anastomosis was situated 2–3 cm proximal to the dentate line. Martin and colleagues[15] recommended that the transitional epithelium of the columns of Morgagni be preserved 'to initiate reflex closure of the sphincters' and thus to ensure continence of liquid stool both during the day and at night. These authors performed the ileo-anal anastomosis at the dentate line in three patients only, but stopped making the anastomosis at that level because all three patients experienced varying degrees of soilage, which was severe enough in one patient to necessitate the establishment of a permanent ileostomy. However, the operative technique used by Martin *et al.* differs from ours in that they have continued to perform mucosal proctectomy, with a 'sleeve' type of endo-anal anastomosis, both in order to remove colitic rectal mucosa and in the belief that the muscular wall of the rectum which they preserve possesses an important proprioceptive function that enhances the quality of continence by enabling the patient to differentiate stool from flatus. Our own philosophy is similar to theirs, but we prefer the greater simplicity of the end-to-end anastomosis, and find that our patients are well able to discriminate both between flatus and faeces, and between solid and liquid stool.

Finally, what of the potential disadvantages of end-to-end ileo-anal anastomosis? The colitic process might involve the mucosa of the upper anal canal and there could thus be some risk both of persistent colitis and of colitis-carcinoma. Although such fears cannot be ignored, studies of the anal transitional zone[16] above the dentate line were reassuring, in that this zone was seldom involved in the colitic process. Even in patients with total colitis, carcinoma is relatively uncommon, and should thus be rare after removal of all the rectal and colonic mucosa. The tiny cuff of potentially 'at-risk' epithelium in the proximal anal canal is, in any case, easily inspected and biopsied through a proctoscope.

Thus, while it cannot be denied that the use of an end-to-end anastomosis in preference to mucosal proctectomy with endoanal anastomosis involves some degree of risk, the risk would appear to be small and outweighed by the potential benefits to the patient. The whole modern 'sphincter-saving' enterprise represents a compromise, because perfect clinical results are unattainable in these patients. However, in the quest for perfection, preservation of the entire anal canal seems justified, according to the results of this study, and is certainly worthy of further trial.

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Synchronous and 'early' metachronous carcinomas of the colon and rectum

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In a review of cases of colorectal cancer presenting to St. Mark's Hospital over the 16-year period 1970–85, 59 patients were found to have a synchronous carcinoma (3·4 per cent). Although 82 per cent of these synchronous tumours were distal to the splenic flexure (and hence within reach of a 60 cm flexible sigmoidoscope) only 42 per cent were detected pre-operatively: the remaining tumours were noted at surgery (24 per cent) or found incidentally on pathological examination of the resected specimen (34 per cent). Histological examination of these synchronous lesions revealed a high proportion with favourable stage (Dukes' A – 75 per cent) and grade (well or moderate differentiation – 90 per cent). Over the same 16-year period, 10 patients presented with an 'early' metachronous lesion (<3 years from initial surgery). Review of these cases noted negative findings on the initial barium studies in four patients and a failure to conduct full examination of the colon at initial presentation in the remaining six. It is concluded that full examination of the colon in all patients presenting with primary colorectal cancer is mandatory and that, in the light of this experience and recent reports in the literature, this should be by pre- or peroperative colonoscopy.

Keywords: Multiple colorectal neoplasms, synchronous carcinoma, metachronous carcinoma, colonoscopy

It is well known that patients with primary colorectal carcinomas may have more than one malignant lesion within the colon and rectum at the time of initial presentation. Studies from St. Mark's hospital more than 10 years ago drew attention to this problem and made certain recommendations with regard to management[1,2]. Many reports have subsequently appeared in the literature noting an incidence of synchronous colorectal carcinomas of between 2 and 9 per cent[3–9]. We wish to report the further experience from St. Mark's, since 1970, with particular reference to the problem of the 'missed' synchronous (early metachronous) tumour.

Patients and methods

All patients presenting to St. Mark's during the period 1970–85 and found to have more than one malignant colorectal neoplasm, were included in this study. Patients with synchronous carcinomas complicating ulcerative colitis or familial polyposis coli were excluded. From the clinical records a standard proforma was completed noting details of the patients' age and sex, presenting symptoms and findings on clinical examination. The results of rigid and flexible endoscopy together with contrast radiology were also noted.

Both the histological stage and grade of the primary or 'index' cancer were recorded and a note made of whether the synchronous tumour was detected in the pre-operative period, at surgery, or incidentally on pathological examination of the resected specimen. To be considered a synchronous neoplasm the criteria noted by Kaibara *et al.* were used[6], i.e. a definite histological picture of malignancy, distinctly separate from the other tumour by intact bowel wall and clearly not of metastatic origin from another colorectal tumour.

In order to study synchronous tumours which may have been overlooked at the time of initial surgery, all patients presenting over the same period of time with an 'early' metachronous tumour (<3 years from surgery) were also studied. As with the synchronous neoplasms, details were recorded of the site of the tumour, the histological stage and grade and the means by which the entire colon and rectum had been assessed for neoplastic lesions at the time of initial presentation. Within this latter group of 'early' metachronous tumours, only those patients who had undergone both operations at St. Mark's Hospital were considered.

Results

Within this 16-year period, 1756 patients presented with a primary malignant colorectal neoplasm and of these 59 (3·4 per cent) had a synchronous carcinoma. Details of the patients' age and sex are included in *Table 1*.

The distribution of the synchronous neoplasms together with the index cancer is shown in *Table 2*. The expected predominance of rectal and rectosigmoid lesions was confirmed.

Table 1 *Synchronous colorectal tumours: St. Mark's experience, 1970–85*

Total no.	59 (3·4 per cent of total)
Men	36
Women	23
Mean age	63·5 years (range 32–84 years)

Table 2 *Anatomical distribution of 59 synchronous colorectal tumours*

	Primary 'index' tumour		Synchronous tumour	
	n	%	*n*	%
Caecum	0		4	(7)
Ascending colon	5	(8·5)	3	(5)
Transverse colon	3	(5)	4	(7)
Descending colon	2	(3)	7	(12)
Sigmoid colon	13	(22)	24	(41)
Rectum	36	(61)	17	(29)

Table 3 *Means by which the synchronous tumours were detected in 59 patients*

Method	*n*	%
Pre-operative assessment	25	(42)
Incidental finding at surgery	14	(24)
Noted on resected specimen	20	(34)

Table 4 *Histological stage and grade of 59 synchronous and primary 'index' tumours*

	Primary tumour		Synchronous tumour	
	n	%	*n*	%
Dukes'				
A	16	(27)	44	(75)
B	18	(30)	10	(17)
C	25	(42)	5	(8)
Grade				
Well	14	(24)	26	(44)
Moderate	40	(68)	27	(46)
Poor	5	(8)	6	(10)

Almost 70 per cent of the synchronous neoplasms also occurred within this region.

The means by which the synchronous carcinomas were detected is shown in *Table 3*. Full assessment of the whole colon, in the pre-operative period, either by contrast radiology or colonoscopy, was performed in only 38 patients (64 per cent). Synchronous tumours were identified pre-operatively in less than one-half of the patients studied and over one-third were discovered incidentally on the resected specimen. Only 49 per cent of synchronous tumours were palpable at laparotomy.

The histological staging and grading of the synchronous carcinomas is noted in *Table 4*. The majority of lesions were favourable; fully 75 per cent being Dukes' A lesions and 53/59 (90 per cent) being well or moderately differentiated.

In all, over the same 16-year period, 35 patients presented with metachronous tumours. Although the time interval in some cases was many years, 37 per cent presented within 5 years of the initial surgery and 10 patients (forming the 'early' metachronous group) occurred within 3 years. *Table 5* records the Dukes' classification and histological grading of all 35 metachronous carcinomas. Unlike the synchronous tumours presenting over the same period, the metachronous tumours were less likely to be confined to the bowel wall and over one-third were associated with lymph node involvement.

Table 6 notes the site of primary and metachronous tumour, together with the time interval, in the 'early' metachronous group. It is worth noting that all but one of the initial tumours had been within the rectum. In four cases barium studies had been performed and considered normal but in the other six patients no investigations of the large bowel had been conducted. Of these ten 'early' metachronous tumours only two were Dukes' A and four patients had associated lymph node involvement at the time of surgery.

Discussion

'No operation for cancer of the large bowel should be done without thorough investigation of the whole large bowel'; this advice remains as true today as when first suggested in 1972[2]. The pre-operative detection of synchronous neoplasms not only allows an appropriate surgical strategy to be adopted but facilitates the planning of a logical policy for follow-up. Since the work of Heald and others in the early 1970s[1,2], there have been major improvements in the techniques available for detecting synchronous neoplasms, e.g. double contrast barium radiology and colonoscopy. It therefore seemed appropriate to review the further experience of synchronous carcinomas at St. Mark's Hospital.

Although the overall incidence of 3·4 per cent for synchronous carcinomas in this series is largely in agreement with other studies[3–7], several authors have recently suggested that the true incidence is higher, i.e. 7–9 per cent[8,9]. The importance of detecting these synchronous lesions at the time of surgery is exemplified in *Table 4* where 75 per cent of the synchronous carcinomas were Dukes' A, an observation confirmed by other workers[6,10]. In view of the early stage of the majority of these lesions it is not surprising to find that 49 per cent were impalpable at laparotomy; if these lesions are to be detected at the time of initial surgery, then means other than the surgeon's hand must be adopted.

It is disappointing to note that only 64 per cent of cases had undergone full assessment of the colon by either contrast radiology or colonoscopy. Interestingly, of those 21 cases that were not fully assessed, all but three had a primary carcinoma of the rectum. It is likely in several cases that a barium enema could not be performed adequately because of an obstructing lesion or inability to retain barium in association with the distressing symptoms caused by the underlying carcinoma. Nevertheless, if this is the case, then a postoperative examination remains mandatory.

The patients in this series are, by virtue of referral patterns, highly selected and it is not unreasonable to assume that the proportion of patients presenting with acute large bowel obstruction in a non-specialist centre will be higher than at St. Mark's Hospital. This being the case, it is likely that many patients presenting at an acute stage do not have full assessment

Table 5 *Histological stage and grade of 35 metachronous tumours together with initial primary tumours*

	Primary tumour		Metachronous tumour	
	n	%	*n*	%
Dukes'				
A	10	(29)	7	(20)
B	17	(49)	15	(43)
C	8	(23)	13	(38)
Grade				
Well	12	(33)	10	(29)
Moderate	20	(57)	18	(51)
Poor	3	(9)	7	(20)

Table 6 *Details of the 10 'early' metachronous tumours*

	First tumour	Comment	Second tumour	Time interval (years)
1	Rectum	No enema	Caecum	3
2	Rectum	No enema	Transverse colon	2
3	Rectum	Enema negative	Descending colon	3
4	Rectum	No enema	Rectum	3
5	Ascending colon	Enema negative	Rectum	2
6	Rectum	No enema	Sigmoid	3
7	Rectum	Enema negative	Caecum	1
8	Rectum	Enema negative	Transverse colon	3
9	Rectum	No enema	Sigmoid	1
10	Rectum	No enema	Transverse colon	3

(Dukes' classification for 10 early metachronous tumours: A, 2; B, 4; C, 4) of their colon at the time of surgery and a careful search of the colon in the early postoperative period is advisable.

In the light of accumulating evidence to support the polyp–cancer sequence and knowledge of the growth rate of polyps[11], it is not unreasonable to propose that the patients presenting with an early metachronous lesion, within 3 years of surgery, harboured a significant lesion at the time of initial presentation. Several series note a bimodal distribution of metachronous tumours with the early peak representing 'missed' synchronous lesions. Heald[2] found 18 missed synchronous tumours in his earlier St. Mark's series. Similarly, other workers studying the incidence of metachronous tumours have noted a high proportion occurring at an early stage in the postoperative surveillance period. In a study from the Mayo Clinic, Agrez *et al.*[12] found 50 per cent of their tumours developed within 5·5 years and Kiefer *et al.*[13] found 40 per cent presenting within 2 years. Such 'missed' tumours seem consistently to be of a more advanced stage[6] – a point confirmed in this present series where only 20 per cent of early metachronous tumours were Dukes' A compared with 75 per cent in the synchronous group.

It can be seen from *Table 6* that all but one of the patients with an early metachronous lesion had initially presented with a rectal carcinoma. It seems, therefore, from this subgroup together with those patients with synchronous tumours in association with rectal primaries previously noted, that the policy to assess the whole colon most often fails in patients presenting with a rectal primary. Figures from St. Mark's for 1985 (J. K. Ritchie, unpublished observations) reveal failure to assess the colon in 38 per cent of patients presenting with a primary rectal carcinoma.

Although the last decade has seen many improvements in contrast radiology, and in particular the introduction of air contrast studies, there are few studies comparing this with direct endoscopic visualization of the colon. There is little doubt that significant lesions are missed on barium examination. In one recent series[8] only 2 of 18 synchronous tumours were noted; similarly Reilly *et al.*[9], in assessing the role of colonoscopy, noted that 60 per cent of endoscopically curable lesions and 11 of 14 multiple cancers were missed on double contrast barium studies. Details of the radiological techniques were not clear from these papers and it is worth noting the excellent results in the hands of enthusiasts[14–16].

The results obtained with routine pre-operative colonoscopy in patients with a primary colorectal neoplasm are encouraging: not only are synchronous carcinomas successfully identified but any polyps noted can either be removed at the time of endoscopic examination or included in the surgical resection[17–19]. If a stenosing lesion prevents full examination (15 per cent in one recent series[18]) then the technique of intra-operative colonoscopy can be adopted[20–22]. Our own preliminary experience with this technique would suggest that full examination of the colon is possible in the majority of cases and that it adds approximately 15–20 min to the total operation time. Finally, there appears to be an increasing role for colonoscopy in postoperative surveillance for early recurrence or true metachronous carcinoma, particularly if initial investigations have revealed synchronous carcinomas or polyps[23,24].

Over the past 25 years there has been little change in the cure rate of colorectal cancer. Favoured approaches at present are the early detection of disease and screening of various high risk groups. We conclude that patients presenting with an established carcinoma are themselves at risk of harbouring a synchronous tumour. The policy to assess the whole colon has failed in the past almost exclusively in patients with a primary carcinoma of the rectum and, with the advent of good-quality double contrast radiology and colonoscopy, all synchronous carcinomas should be detected and treated appropriately and the 'missed' synchronous tumour should be a thing of the past.

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Submucosal versus ligation excision haemorrhoidectomy: a comparison of anal sensation, anal sphincter manometry and postoperative pain and function

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Submucosal (SM) and ligation excision (LE) haemorrhoidectomy were compared to establish whether SM is a less painful procedure and whether anal sensation is better preserved by SM, and, if so, how this relates to postoperative function. There were 18 SM and 22 LE patients. Anal sphincter manometry and anal mucosal electrosensitivity were measured pre-operatively and 6 weeks after surgery. Postoperative pain was assessed by linear analogue scale. Anal sphincter pressures which were high pre-operatively fell to normal after surgery. Neither operation affected functional sphincter length or the recto-anal inhibitory reflex. Forty per cent of patients showed ultraslow waves on sphincter motility studies. These were associated with the highest pressures and in all but three cases disappeared after surgery. There were no differences in postoperative pain scores between the two techniques but there was a wide range from no pain to very severe pain in both groups. Submucosal haemorrhoidectomy preserved anal sensation better than ligation excision but this was not reflected in improved function. There was minor leakage and soiling in 50 per cent of patients from both groups and two SM and LE patients had initial faecal incontinence. All these symptoms had resolved by 6 weeks.

Keywords: Haemorrhoidectomy, submucosal, ligation excision, postoperative pain, anal mucosal electrosensitivity, anal sphincter manometry

Haemorrhoidectomy is considered to be a painful operation[1–3]. Parks[1] suggested that patients will conceal rectal bleeding because of the dread of an operation. He considered that the widely used operation of low ligation and excision[4] involved ligation of the sensitive anal mucosa and, furthermore, pain was caused by large areas of denuded anal wall leading to spasm and painful bowel actions. He advocated a submucosal haemorrhoidectomy on the grounds that the haemorrhoidal tissue was ligated above the anorectal ring and the mucosal lining was preserved resulting in a less painful procedure.

In this study we measured anal sphincter pressures, anal mucosal sensation and postoperative pain scores to assess whether, in our hands, submucosal haemorrhoidectomy conferred any advantage over the ligation excision technique. We posed two questions: firstly, is submucosal haemorrhoidectomy a less painful procedure, and secondly, is anal sensation better preserved by this operation and, if so, how does this relate to postoperative function?

Patients and methods

To answer these questions 43 patients were allocated to either a submucosal or ligation excision haemorrhoidectomy. The allocation of operation was random. These patients all had prolapsing haemorrhoids which had failed to respond to conservative measures. Two authors performed the operations (D.C.C.B. and K.D.V.). Three patients did not attend for postoperative assessment. This left 18 in the submucosal (SM) group, 13 men and 5 women, median age 51 years (range 35–70 years) and 22 in the ligation excision (LE) group, 12 men and 10 women, median age 58 years (range 32–74 years). The submucosal operation was performed using a Parks anal retractor opened to a maximum of three fingers' breadth; the haemorrhoidal tissue lying between the blades of the retractor was infiltrated with 1 in 300 000 adrenaline in saline and the technique followed that described by Parks. The mucosal flaps were sutured to the top of the internal anal sphincter with 3 x 3/0 Vicryl (Ethicon Ltd, UK) sutures at the end of the procedure[1]. In the ligation excision operation, the tissues were infiltrated with 1 in 300 000 adrenaline in saline, an anal dilatation was not performed, and the operation followed the description of Milligan *et al.*[4], except that the haemorrhoidal tissue was ligated above the dentate line.

Sphincter manometry. Pre-operative sphincter manometry was performed using a precalibrated water-filled closed system consisting of a detecting probe 4 mm in diameter attached by a non-distensible polyethylene tube to a transducer (Statham 230B, Gould Medical Ltd, Coventry, UK) connected via an amplifier (Hewlett Packard 7888A, Waltham, Massachusetts, USA) to an eight-channel recorder (Hewlett Packard, Waltham, Massachusetts, USA). Maximum resting and maximum voluntary contraction pressures were recorded. Sphincter length was assessed by the length of the high pressure zone. The recto-anal inhibitory reflex was elicited by inflating a rectal balloon with air in increments of 10 ml for periods of 60 s. The lowest volume required to inhibit recovery of the internal sphincter tone for 1 min was recorded.

Anal sensation. Anal sensation was measured using the technique of anal mucosal electrosensitivity[5]. The catheter consisted of a 10 F.G. Dover catheter graduated in centimetres with two platinum electrodes 1 cm apart towards the tip. Copper wires connected to the electrodes passed to a constant current generator (Department of Medical Physics, Bristol Royal Infirmary) supplying square wave stimuli of 100 μs duration at 5 pulses per second. The electrosensitivity probe was lubricated with equal volumes of KY jelly (Johnson and Johnson) and normal saline and introduced into the anal canal with the patient in the left lateral position. The current across the electrodes was increased incrementally in fractions of a milliamp (mA), until a threshold of sensation was reported by the patient. Three recordings and a mean value were obtained at each of three equidistant sites in the upper, middle and lower zones of the functional sphincter.

Postoperative pain. Postoperative pain was assessed using a linear analogue scale. Each patient was given a chart (*Figure 1*) and asked to record on the first five postoperative days the average amount of pain throughout the day. The pain was scored on a scale of 1 to 10, 1 being no pain and 10 the worst pain the individual had ever experienced.

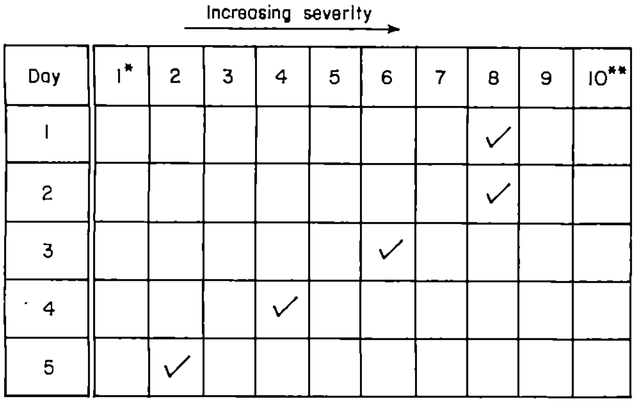
Postoperative function. Watts *et al.*[2] reported that anal wounds from different types of haemorrhoidectomy had all healed by 6 weeks. The patients were therefore interviewed at 6 weeks and assessment made of anal continence, in particular loss of discrimination between flatus and faeces, leakage or soiling and incontinence to liquids and solids. At this stage the anorectal physiology studies were repeated.

Control studies. Manometry studies and mucosal electrosensitivity studies were undertaken in 20 control subjects. These were patients who had no gastrointestinal disease. There were 15 women and 5 men, median age 56 years (range 19–80 years).

Statistical analysis and ethical considerations. The statistical significance of data compared in this study was evaluated using the Mann–Whitney *U* test for unpaired data and Wilcoxon signed ranks test for paired data. Informed consent was obtained from each patient. The study was approved by the ethical committee of the Bristol and Weston Health Authority.

Results (*Table 1*)

Manometry. There were no significant differences in functional sphincter length or recto-anal inhibitory reflex between either group and controls pre-operatively. Haemorrhoid patients had raised resting pressures compared with controls ($P < 0.00001$, *Figure 2*). Ultraslow waves (*Figure 3*) were seen in 16 patients, 40 per cent of the total (9 men, 7 women). Nine of these were in the SM group and seven in the LE


Increasing severity

Day	1*	2	3	4	5	6	7	8	9	10**
1								✓		
2								✓		
3						✓				
4				✓						
5		✓								

Figure 1 *Linear analogue scale for assessment of postoperative pain.* * *No pain,* ** *worst pain ever experienced*

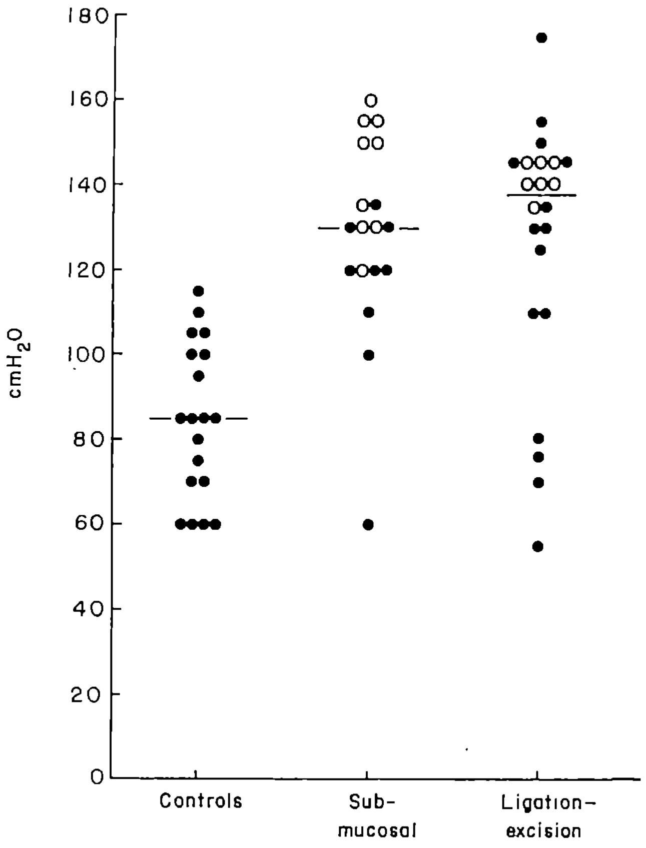


Figure 2 *Anal sphincter manometry. Haemorrhoid patients had raised resting pressures, and ultraslow waves* (○) *were associated with the highest pressures*

Table 1

	Controls	Submucosal Pre-operative	Submucosal Postoperative	Ligation excision Pre-operative	Ligation excision Postoperative
Functional sphincter length (cm)	3·5 (3·0–4·0)	4·0 (3·0–4·5)	4·0 (3·0–5·0)	4·0 (3·0–5·0)	3·75 (2·5–5·5)
Maximum resting pressure (cmH$_2$O)	85 (60–115)	130 (60–160)	88 (60–140)*	138 (55–175)	103 (45–155)*
Maximum voluntary contraction pressure (cmH$_2$O):					
Men	285 (200–290)	360 (155–500)	370 (165–450)	295 (225–575)	400 (300–525)**
Women	158 (110–285)	235 (205–288)	210 (213–275)	210 (145–300)	165 (95–225)*
Recto-anal inhibitory reflex (volume to inhibit for 1 min, ml)	50 (10–140)	80 (60–140)	70 (30–200)	75 (30–180)	75 (40–180)
Anal mucosal electrosensitivity (mA):					
Upper anal canal	5·7 (3·3–7·3)	9·3 (4·3–18·0)	8·0 (4·0–14·0)	9·3 (3·3–15·6)	9·0 (4·0–>25)
Middle anal canal	4·2 (2·0–6·0)	7·0 (4·0–13·3)	5·3 (2·7–10·3)***	5·1 (3·0–11·3)	6·7 (3·0–15·0)
Lower anal canal	4·8 (3·0–7·0)	6·3 (4·0–9·0)	5·1 (2·6–10·3)**	5·8 (3·0–7·6)	6·0 (3·0–13·0)
Pain scores (days) (medians and ranges)					
1			8 (1–10)		5 (1–10)
2			6 (1–10)		5 (1–9)
3			7 (1–10)		5 (1–9)
4			4·5 (1–10)		4 (1–9)
5			3 (1–10)		4 (1–10)

*$P < 0·01$ *versus* pre-operative, **$P < 0·05$ *versus* pre-operative; ***$P < 0·02$ *versus* pre-operative

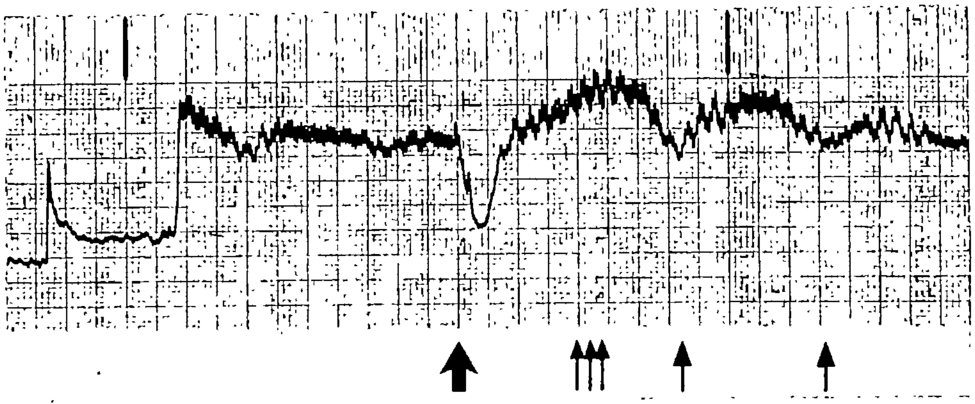


Figure 3 *Anal sphincter pressure profile in haemorrhoid patients. There is a spontaneous recto-anal inhibitory reflex (large arrow). Slow waves (small arrows) and ultraslow waves (medium arrows) are seen*

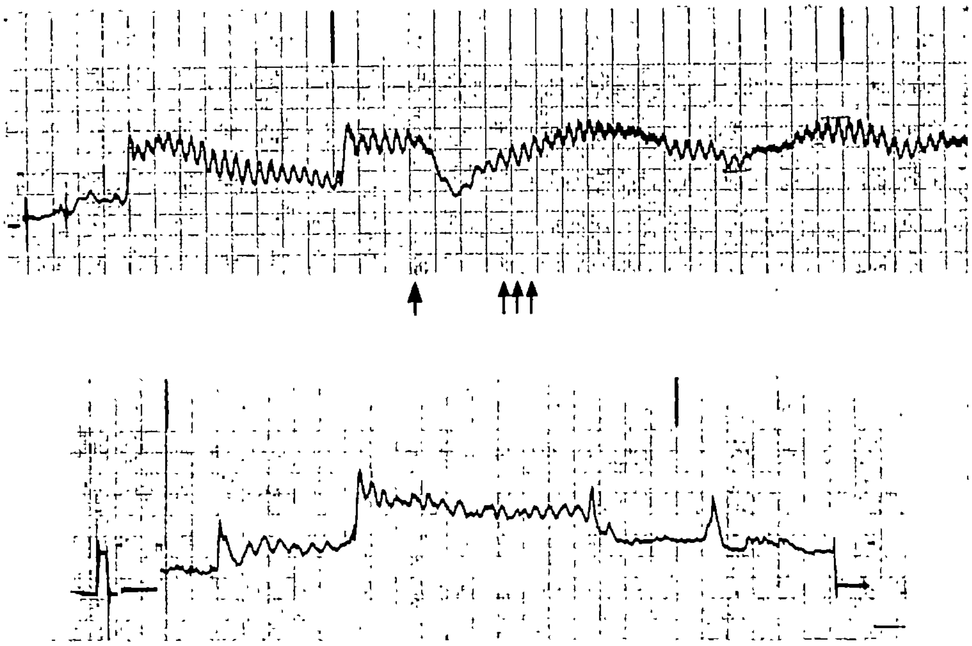


Figure 4 *Above, pre-operative pressure profile showing ultraslow waves with reflex (medium arrow) and slow waves (small arrows). Below, postoperative trace showing disappearance of ultraslow waves but persistence of slow waves*

group. These ultraslow waves were associated with the highest pressures; median for the patients with ultraslow wave 143 cmH_2O, those without 120 cmH_2O. Maximum voluntary contraction pressures were higher in male controls than females ($P<0{\cdot}02$); therefore the results of males and females were considered separately for this parameter.

Postoperatively, both haemorrhoidectomy techniques reduced resting pressures into the normal range but did not affect functional sphincter length or recto-anal inhibitory reflex. Of the 16 patients with ultraslow waves, only 3 still had ultraslow waves present postoperatively and in these patients the reduction in pressure achieved by the operation was small (145–130, 155–130, 155–140 cmH_2O) (*Figure 4*), Surprisingly, although SM did not affect maximum voluntary contraction, men undergoing LE had increased contraction pressures whilst women had reduced pressures after operation.

Anal sensation. Both pre-operative haemorrhoid groups showed higher sensory thresholds in the upper sphincter. SM haemorrhoidectomy resulted in reduced sensory thresholds with heightened sensation. This was significant at the middle ($P<0{\cdot}02$) and lower ($P<0{\cdot}05$) sites in the anal canal. LE produced no significant changes in sensory thresholds.

Postoperative pain. There were no differences in the amount of postoperative pain between the two techniques. SM was painful on the first day with a median score of 8 gradually reducing to 3 by the fifth day. LE had a median score of 5 initially remaining fairly constant with a score of 4 by the fifth day. However, there was a great variation between patients with some patients from either groups experiencing no pain or very severe pain on each of the first five postoperative days. The most severe pain was often associated with the first bowel action but there were no differences in the time of first bowel actions between the two operations.

Postoperative function. Anal leakage or soiling was common and occurred in 50 per cent of both groups (9 SM and 11 LE). Only two patients in each group complained of episodes of frank incontinence to liquid or solid stool. Five LE patients and two SM patients had some loss of rectal discrimination between flatus and faeces. In all patients these disturbances of continence had resolved by the time of interview at 6 weeks when all patients were normally continent.

Discussion

There were no differences in postoperative pain between the two procedures in this study. This concurs with the findings of Watts *et al.*[2], but Singh and Lal[6] reported severe pain after submucosal haemorrhoidectomy only on the day of operation after which it was less painful than ligation excision over the next few days. Parks found that 66 per cent of patients after SM had less than average or almost no pain[1,7]. The reasons for these reported differences are not clear; we performed the SM operation as described by Parks, but there was a wide range of pain in both groups. Watts *et al.*[2] considered that an individual reaction to pain is probably more important than the technique of operation used. But what causes pain in those experiencing it? It seems unlikely to be ligation of sensitive epithelium as SM has conferred no advantage. Spasm in the sphincters has been implicated and some surgeons perform an internal sphincterotomy[8,9] or dilate the sphincters at operation but this has not conferred any advantage[3]. Denuded areas of anal canal may be responsible for producing pain as proposed by Parks as even with the SM operation Watts *et al.*[2] reported that small open wounds were often present in the anal canal at 10 days.

Hancock and Smith[10,11] concluded that there was an underlying overactivity of the internal anal sphincter causing haemorrhoids and this was responsible for the raised resting pressures that are found. Read *et al.*[12] disagreed with the above concept. They found that pressures were reduced by haemorrhoidectomy whether or not this was preceded by anal dilatation and considered it more likely that increased sphincter tone was maintained by the presence of the haemorrhoidal masses because of reflex tonic contraction of the internal and external anal sphincters. The findings in this study would tend to support the latter view. Anal dilatation was not performed before the LE operation whilst some degree of dilatation must occur following the introduction of the speculum in the SM operation but this was minimal. Nevertheless, only one parameter of internal sphincter function was affected by both operations: the maximum resting pressure returned to normal but functional sphincter length and recto-anal inhibitory reflex remained unchanged. This would infer that it is the haemorrhoidal tissue itself which is responsible for the increased pressure.

Forty per cent of patients in this study were found to have ultraslow waves, a similar incidence to that reported elsewhere[11,12]. Hancock[11] considered ultraslow waves to represent a synchronous contraction of the whole internal sphincter. In this study ultraslow waves were associated with higher pressures and often a pulse wave was superimposed indicating the vascularity of the haemorrhoidal tissue in these patients. Hancock[11] found that slow waves were of faster frequency lower in the sphincter and may be responsible for emptying the anal canal. It is possible that ultraslow waves represent some form of peristaltic action in the sphincters induced by the presence of the haemorrhoidal tissue.

A high incidence of temporary soiling and leakage was produced by both procedures in this study with half the patients in each group affected. By 6 weeks they were all normally continent. Bennett, Friedman and Goligher[13] after LE operation reported an incidence of 26 per cent minor defects of anal control. Thomson [14] considered that the anal cushions contributed to the mechanism of anal closure and fine control of continence, explaining the high incidence of impairment of continence following haemorrhoidectomy particularly by the Whitehead method[15] where there is circumferential stripping of the anal lining (Read *et al.*[12]). Read *et al.*[12] suggested that because the incidence of severely impaired continence was so low after haemorrhoidectomy, the integrity of the vascular cushions and normal anal sensation are not critical factors for maintaining normal continence. This was reinforced by their observation (Read and Read[16]) that anaesthetizing the anal canal with lignocaine gel did not impair continence. We have found that lignocaine gel does not abolish anal sensation completely, but roughly doubles the electrosensitivity threshold (A. M. Roe, personal observation). Anal sensory thresholds were higher in the upper anal canal pre-operatively compared with controls. We have previously reported this and suggested it was due to less sensitive rectal mucosa being displaced into the upper sphincter as the haemorrhoidal cushions slide down[5]. In the cases undergoing SM haemorrhoidectomy, the thresholds of sensation in the middle and lower anal canal fell after surgery. This is most likely to be due to preservation of the sensitive anal skin and relocation to its normal site. In the LE group, sensory thresholds were unchanged. Although, in our hands, submucosal haemorrhoidectomy was no less painful, we were able to confirm Parks' original objective of preserving anal sensation. This was not associated with any significant improvement in function at 6 weeks.

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Left intrahepatic cholangio-enteric anastomosis (round ligament approach): an effective palliative treatment for hilar cancers

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Palliation of obstructive jaundice in patients with hilar cancer can be achieved either by surgical bypass or by intubation and drainage. A simple and effective technique is presented which gives excellent palliation without the need for tubes or stents: left intrahepatic cholangio-enteric anastomosis, using the duct of segment III (i.e. the inferolateral segment of the left liver). The procedure is performed by using the round ligament approach to the duct of segment III in the base of the umbilical fissure. A defunctioned loop of jejunum is then anastomosed to this duct. Over a period of 25 years, 48 patients with hilar cancer had this procedure in this unit. The operative mortality (death within 2 months) was 6 per cent and the complication rate was 17 per cent. Seventy-three per cent of patients had complete relief of jaundice and a further 23 per cent had partial relief. The mean survival was 9·2 months and the quality of life was excellent. These data suggest that this is a very satisfactory palliative technique for patients with hilar cancer who are not suited for radical tumour excision.

Keywords: Hilar cancer, biliodigestive anastomosis, Klatskin tumour, obstructive jaundice

Malignant obstruction of the hilar area of the liver can result from a number of causes. The most common cause is hilar cholangiocarcinoma (Klatskin tumour), but gallbladder carcinoma, primary or secondary liver tumours, or certain gastric or pancreatic cancers can also be responsible. All of these tumours pose a similar management problem, i.e. the relief of obstructive jaundice. Surgical resection offers the best hope of prolonged survival and should always be considered first when dealing with these tumours. However it is rarely possible to perform an oncologically acceptable resection and palliative liver resection is inappropriate. In such situations satisfactory relief of jaundice should still be a realistic objective and a great many techniques have been described to relieve jaundice. In 1957 Soupault and Couinaud[1] described a simple technique for bypassing a malignant hilar obstruction by anastomosing a jejunal limb to the duct of segment III on the left side of the liver (i.e. the inferolateral segment of the left liver). Because this duct is identified by following the round ligament into the recessus of Rex in the umbilical fissure this technique has become known as the round ligament approach to the duct of segment III. It provides good decompression of the obstructed intrahepatic biliary tree without the need for external or internal tubes, stents or appliances, and has been the favoured surgical bypass technique for hilar cancer in this unit for many years.

Patients and methods

Technique of left intrahepatic cholangioenteric anastomosis

The operative details of the round ligament approach to the duct of segment III have been described in a previous communication from this unit[2]. The round ligament is first divided and then freed from the liver. The ligament is then retracted downwards and to the right, thus exposing the umbilical fissure between segment III and IV (*Figure 1*). It is necessary to enlarge this fissure by dividing the parenchyma just to the left of the falciform ligament for a distance of 3–5 cm. The left margin of the round ligament is thus freed down to its base until its sheath expands to implant into the umbilical venous recess. The branch of the portal vein to segment III is easily recognized as it arises from the left corner of the recess. The bile duct to segment III lies posterosuperiorly to the portal vein branch and identification can be aided by the use of a needle and syringe. The duct is then dissected and incised longitudinally for a distance of at least 1 cm. Next a long (50 cm) defunctioned jejunal loop is prepared, Roux-en-Y, and brought up through the transverse mesocolon. An end-to-side anastomosis is performed between the jejunal limb and the bile duct to segment III (*Figure 1*), this being preferable to a side-to-side anastomosis because of space constraints in the umbilical fissure. The lumen of the jejunum is first closed across half of its diameter (mesenteric half) and the antimesenteric half is then anastomosed to the bile duct using interrupted monofilament sutures (5/0 nylon or synthetic absorbable). A transanastomotic drain is generally left in place to allow postoperative cholangiography and is usually removed at 2–3 weeks.

Patients

Over a period of 25 years, 48 patients with hilar cancer had a left intrahepatic cholangio-enteric anastomisis performed by the senior author (H.B.) using the round ligament approach. The majority of these patients were operated on in the last 10 years since this technique was adopted in this unit as the surgical bypass procedure of choice for unresectable hilar cancers. There were 27 men and 21 women with a mean age of 58 years (range 34–74 years); 24 patients had a Klatskin tumour, 18 had gallbladder carcinoma and 6 patients had hilar extension of liver, gastric or pancreatic tumours. All patients were considered unsuitable for radical tumour resection either because of advanced age/poor general condition, or because of adverse tumour factors (extensive spread within the liver, regional or systemic spread, lymph node involvement outside the hepatic pedicle, or involvement of the main trunks of the portal vein or hepatic artery). The mean bilirubin level in these patients was 331 μmol l^{-1} (range 27–1361 μmol l^{-1}). The mean duration of jaundice was 3 months.

Results

Three patients died during the first two postoperative months, giving a perioperative mortality rate of 6·3 per cent. Complications occurred at some time between the surgical procedure and the death of the patient in eight cases

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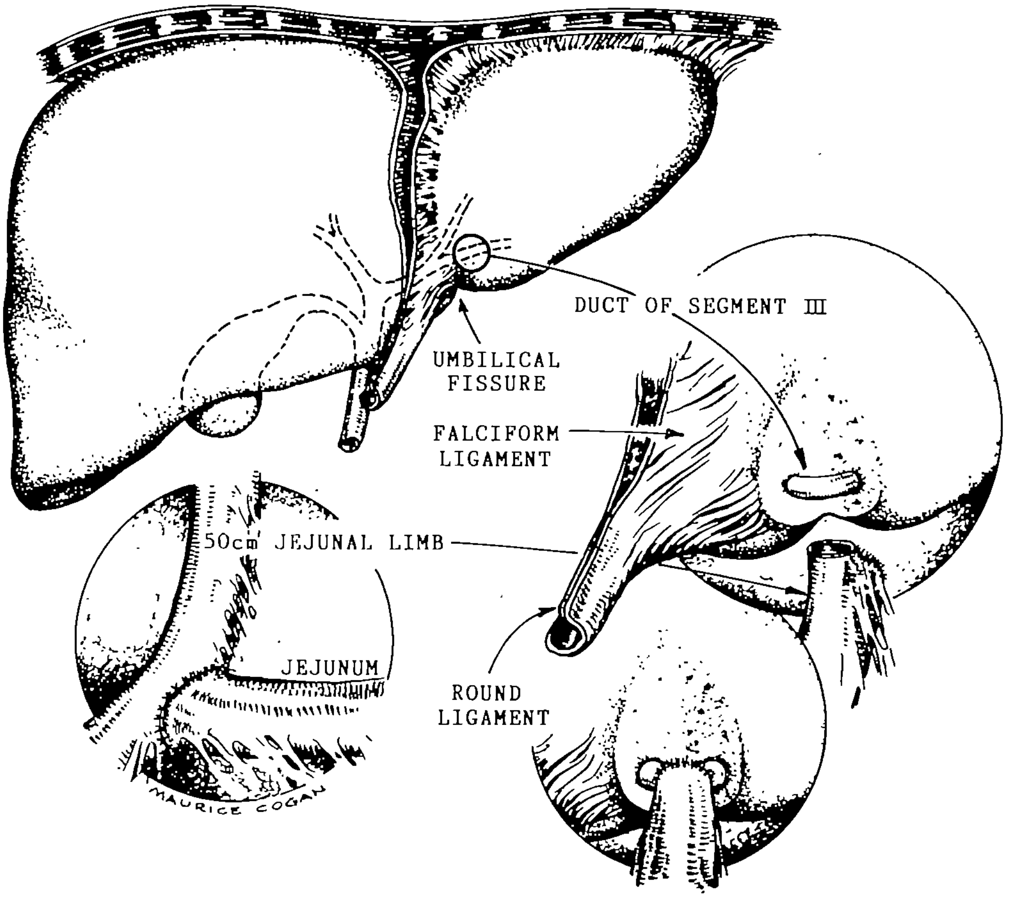

Figure 1 *Technique of round ligament approach to the duct of segment III*

(17 per cent). Four patients had leaks through their bilio-enteric anastomosis. One of these required reoperation and the other three ceased spontaneously over 2–3 weeks. Two patients developed attacks of cholangitis, and two had a pulmonary embolism (one fatal). Thirty-five patients (73 per cent) had complete relief of jaundice (i.e. return of bilirubin level to within the normal range). Eleven patients had partial relief of jaundice (i.e. reduction of bilirubin by at least 50 per cent compared with pre-operative values). Two patients had less than 50 per cent reduction in their serum bilirubin. The mean survival was 9·2 months (maximum survival 19 months). The mean duration of well-being (i.e. free from jaundice and other symptoms) was 8·4 months, giving a 'comfort index' (i.e. duration of well-being expressed as a percentage of total survival) of 91 per cent.

Discussion

The ideal treatment for malignant obstruction of the hilar area of the liver is radical tumour excision, if necessary accompanied by liver resection. However this is a realistic objective in only 20–30 per cent of patients in most series[3–6], and the majority of patients therefore require an effective palliative procedure to relieve their jaundice. It is important to emphasize that the goal of palliation in these cases is to relieve the patient's symptoms (jaundice, pruritus, malaise), and the effectiveness of all palliative procedures should be judged by their ability to do this rather than by their effect on survival. In choosing a palliative procedure therefore the surgeon must take into account the general condition and life expectancy of the patient (i.e. the risk to the patient); the effectiveness of the various palliative procedures—not only in terms of quality but also in terms of durability; and the risk of introducing new problems into the patient's life (e.g. cholangitis and external devices requiring a high level of nursing care). These factors must be weighed in each case and treatment individualized accordingly. Unfortunately there is no universally suitable palliative procedure.

In our experience the round ligament approach to the duct of segment III gives effective and lasting relief of jaundice in patients with hilar cancer. There is a low mortality and morbidity rate and, most importantly, palliation is achieved without the need for tubes, stents or drains which may themselves cause problems and reduce the patient's quality of life. The technique effectively relieves jaundice and pruritus even when the obstruction is high in the hilar area and the left and right hepatic ducts are separated by tumour. Effective jaundice relief can be achieved by draining 35–40 per cent of the functioning hepatic parenchyma (i.e. the left half of the liver) provided the right half of the liver is not infected. If the right liver is infected as well as obstructed, good palliation will not be possible by draining only the left side. Other situations in which this technique is not appropriate are: extensive metastases in the left lobe of the liver; left lobe atrophy; and involvement of the secondary branches on the left side of the liver. The last two contra-indications are particularly important to recognize because, although a cholangio-enteric anastomosis will be technically feasible in these situations, an inadequate amount of functioning liver parenchyma will be drained to give satisfactory relief of jaundice. In the presence of these contra-indications it would be preferable to perform some other type of drainage procedure.

There has been a recent surge in the popularity of intubation techniques for hilar cancer—either the U-tube placed at laparotomy, or endoprosthesis placed at endoscopy[7–10]. These techniques have the obvious advantage of simplicity, and the tubes are claimed to be relatively easily placed. However the mortality for surgically placed tubes is at least as high for surgical bypass in most series[7,11–13]. The mortality for endoscopically placed tubes is obviously less, but the success of endoscopic placement of endoprostheses is much less for hilar cancers than for tumours lower in the common bile duct, and in addition the use of the endoscope precludes histological confirmation of the nature of the biliary obstruction. All tubes have the disadvantage that they almost invariably become blocked in time, and subsequently infected. For this reason the early advantage of these tubes is frequently bought at the expense of short-lived palliation and the patient is faced with early recurrence of jaundice, blockage of tubes, cholangitis, or the need for daily catheter care. Some patients may live for many months in this condition and we believe that intubation and drainage is a second class form of palliation which is best reserved for very ill patients with a very limited life expectancy. Based on the experience of the present series we therefore conclude that a much more effective palliation can be obtained relatively easily by surgical bypass using the left intrahepatic cholangio-enteric anastomosis (the round ligament approach).

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Contact ultrasonography in the detection of liver metastases from colorectal cancer: an in vitro study

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Occult hepatic metastases (OHM) may be present in a quarter of patients undergoing apparently curvative surgery for colorectal cancer[1].

Apart from the encouraging Glasgow experience of serial ultrasound and CT which detected OHM in >20 per cent of patients[1], the other promising means of detecting OHM is the hepatic perfusion index, which produces a dynamic radioisotope hepatic scan in which the arterial and venous phases of hepatic blood supply are studied and compared with those of the kidney. It seems that patients with an abnormal HPI usually go on to develop obvious hepatic metastases[2].

Intra-operative contact ultrasound (CUS) is a relatively new technique which has been advocated for the detection of occult hepatic metastases. The aim of our study *in vitro* was to try and define the minimum diameter of hepatic metastases which CUS can detect.

Materials and methods

Twenty livers were removed at necropsy within 24 h of death from patients with proven malignant disease and scanned immediately. All patients had histologically confirmed gastric or colorectal adenocarcinoma. The livers were pre-marked with sutures at 1 cm intervals on each side of the liver and these were then connected by parallel intervening sutures (*Figure 1*). The livers were then systematically scanned along these defined planes, the presence of any metastases was noted and their diameter and depth from the liver surface measured. Following imaging the liver was sectioned along exactly the same parallel lines. The number, diameter and site of metastases visible in the cut section was recorded.

The machine used for this study was a Bruel and Kraer type 1846 ultrasound scanner together with 3 and 5 MHz transducers (dual head sector transducer 8529). Both transducers were used although all copies were made with the 5 MHz machine; ultrasound jelly was used to improve contact between the transducer and the liver. Copies of the images were made using an X-ray plate system.

Results

Of the 20 livers imaged 11 were found to contain metastases. The 5 MHz transducer was found to be much more suitable for contact ultrasound scanning of the liver producing much cleaner definition and the reduced depth of imaging was not found to be a disadvantage in this situation. All data and figures relate to the 5 MHz transducer. In four of the livers the number of hepatic metastases was so extensive as to make accurate determination of the number of metastases in some planes impossible and these planes were excluded. In the remaining sections which we imaged 67 metastases were found and 45 of these were detected by CUS (67 per cent); all the metastases appeared hyperechoic (*Figure 2*). Of the 37 metastases of 1 cm in diameter or greater, 95 per cent were detected (*Table 1*). No metastases of <0·5 cm in diameter were detected; 10 of 15 metastases between 0·5 and 0·9 cm were imaged. The measurement of diameter and depth of metastases by CUS was found to be very accurate (to within 1 mm). No false positive scans were produced by CUS. In two livers which were normal to palpation metastases were demonstrated by CUS (0·7 cm diameter at 2·4 cm depth and 1·1 cm at 4·2 cm). The time taken for imaging was between 20 min and 2 h and was longer in livers from patients with multiple metastases, each of which required measurement.

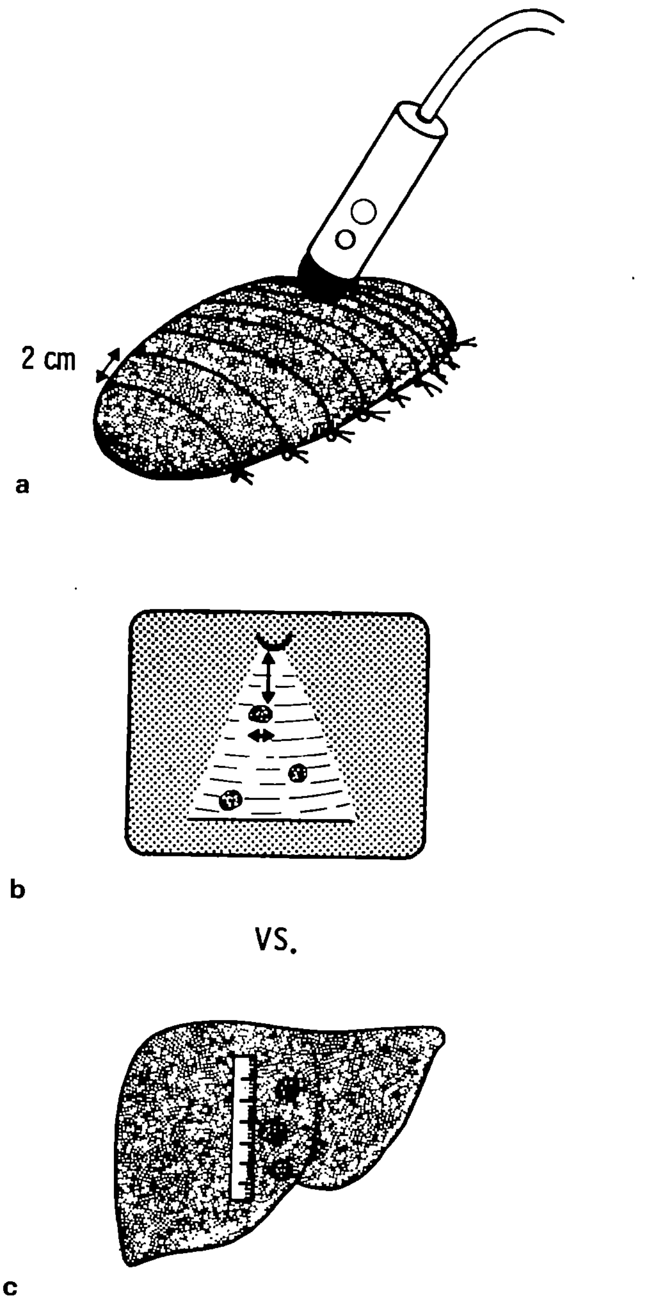

Figure 1 *Diagram of technique:* **a**, *scanning marked planes;* **b**, *measuring diameter of metastases with contact ultrasonography;* **c**, *measuring diameter of metastases with a rule in the same planes after slicing a vertical section of the liver along the planes marked in* **a**

Discussion

Contact ultrasound (CUS) is clearly a potentially important technique for the detection of OHM. Encouraging clinical

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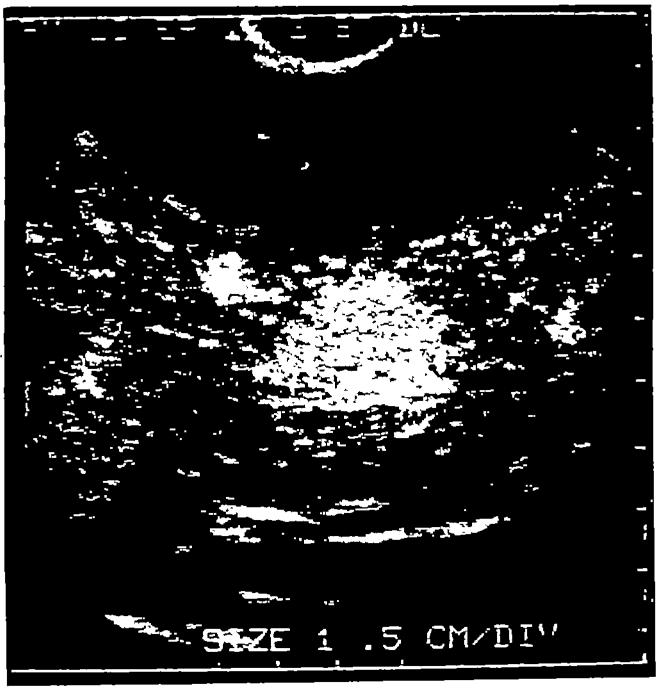

Figure 2 *Photograph of central (white) hyperechoic liver metastases seen with contact ultrasound*

results for contact ultrasound imaging have been reported. Machi *et al.*[3] reported the detection of hepatic metastases in 5 out of 33 patients with colorectal cancer which were missed by pre-operative imaging and palpation at laparotomy. Castaing *et al.*[4] in France have reported encouraging results using a 5 MHz intra-operative ultrasound probe in 98 patients undergoing planned hepatic resection or surgery for their gastro-intestinal primary malignancy. CUS was shown to be considerably more sensitive than arteriography, CT scan or pre-operative ultrasound (3·5 MHz) in detecting metastases of <3 cm in diameter and particularly those of <1 cm. Of the 42 patients with gastro-intestinal malignancies 2 were found to have non-palpable hepatic metastases by CUS. Intra-operative CUS may also have a role during hepatic resection to demonstrate the relationship of tumours to intrahepatic vascular structures[5] and in other pancreaticobiliary operations[6].

In our study *in vitro* CUS was able to detect 95 per cent of lesions >1 cm in diameter and 66 per cent of those between 0·5 and 1 cm. Finlay and McArdle[1] demonstrated that in only 3 of 16 patients with OHM which they detected using CT and ultrasound were the lesions <1 cm in diameter and we would thus expect to detect almost all of these OHM by CUS if this technique is as sensitive *in vivo* as it is *in vitro*. We had no false positive tumours despite our lack of any previous experience of ultrasound imaging.

It is likely that surgeons could easily become proficient in the use of the probe and CUS is likely to be considerably more sensitive than conventional pre-operative scans.

Table 1 *Detection rate of hepatic metastases of differeing diameter*

	Diameter of metastases				
	0–0·4	0·5–0·9	1–1·4	1·5–1·9	>2 cm
Pathology	15	15	14	10	13
CUS	0	10	12	10	13
Detection by CUS (%)	0	66	85	100	100

CUS, contact ultrasonography

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Treatment and outcome in 52 consecutive cases of ampullary carcinoma

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The results of treatment and outcome in 52 consecutive patients presenting to Leicester from 1972 to 1984 are presented. The number of patients diagnosed increased from two per year before the introduction of duodenoscopy to nearly five per year afterwards. Endoscopic drainage (ED) was attempted in 21 patients with a success rate of 81 per cent. In eight cases ED was used pre-operatively and in the remainder as definitive treatment. Twenty-four patients had a Whipple's resection (12·5 per cent mortality), four patients had a local resection (no deaths), ten patients had surgical bypass (60 per cent mortality) and thirteen patients had ED alone (23 per cent mortality). The major risk factor score was significantly greater in patients undergoing surgical bypass compared with Whipple's resection. Age and risk factor scores were significantly greater in patients who had ED drainage alone than in surgical patients. The 5 year survival rate for resection was 56 per cent versus *13 per cent for drainage procedures* ($P<0.001$). *Survival in resection cases was directly related to the degree of tumour differentiation and a new staging system. It is proposed that all patients with ampullary tumours should have endoscopic biopsy followed by ED; Whipple's resection remains the surgical treatment of choice.*

Keywords: Ampulla of Vater, pancreaticoduodenectomy, endoscopy, endoscopic retrograde cholangiopancreatography

Adenocarcinoma of the ampulla of Vater accounts for about 6–12 per cent of all cases of ampullary/pancreatic cancers[1–5]. The mortality rate for Whipple's operation is now of the order of 10–15 per cent[1,3,6–9] or even better[5,10–14] and there are also encouraging trends in long-term survival[5,11,15,16]. Unhappily these developments are not universal—a mortality for Whipple's resection for ampullary tumours of 20–30 per cent continues to be reported in some series[4,17–20]. These poor results have led to renewed interest in local resection of ampullary tumours[20,21], first described by Halstead[22] in 1891.

It is difficult to draw major conclusions from most of these studies, however, because of referral bias[1,6–8,10,14], small numbers[1,2,18,19,21] and retrospective retrieval of cases from numerous hospitals[2,20]. There are surprisingly few single-centre studies that have provided a detailed breakdown of clinical presentation, treatment and outcome for *all* patients within a defined population. The development of predictive risk factors in patients undergoing surgery for biliary tract disease should also allow a more meaningful analysis of the various forms of treatment[23–26]. We report on a consecutive series of 52 patients with ampullary carcinoma presenting to a single centre, detailing the results of surgical procedures and indicating the impact of endoscopy on diagnosis and treatment.

Patients and methods

The details of all patients presenting with a diagnosis of ampullary carcinoma to the two main Leicester Hospitals (850 000 population) between 1972 and 1984 inclusive were reviewed. Clinical, haematological and biochemical data, endoscopic findings and types of treatment and their complications were obtained from case notes. Major and minor laboratory risk factors[23,24,26] and medical risk factors[25] (*Table 1*) were recorded and related to major (life-threatening) postoperative complications.

Endoscopy

Side-viewing endoscopy and endoscopic retrograde cholangiopancreatography (ERCP) for diagnosing ampullary tumours were routinely used from 1976. Endoscopic drainage (ED) of tumour masses was routinely commenced in September 1980. The common bile duct (CBD) was cannulated by the sphincterotome and a long sphincterotomy was made through the tumour mass using blended current[27].

Histopathology

Tumour specimens were subjected to an independent histological review by a pathologist who was unaware of the clinical history of the cases (I.C.T.). Tumour grade was recorded: well differentiated, grade 1; moderately differentiated, grade 2; and poorly or undifferentiated, grade 3. Tumour stage was ascertained according to degree of local invasion: submucosa only, stage I; invasion through the wall of the common bile duct, stage II; invasion of the pancreatic parenchyma, stage III and lymph node involvement, stage IV.

Follow-up

This was achieved up to December 1986 for all patients by clinic attendance or written contact with the patient's consultant and/or general practitioner.

Statistical analysis

Continuous variables were analysed by the Mann–Whitney *U* test. Discrete variables were analysed by the χ^2 test; Yates' correction was employed when the number of expected observations was small. The survival of patients discharged from hospital was determined by the Kaplan–Meier product limit method of life-table estimation, and the

Table 1 *Risk factors used to compare different treatment groups*

Major	Minor	Medical
Bilirubin $>200\,\mu$mol/l	Bilirubin 100–200 μmol/l	Hypertension
Haematocrit $<30\%$	Alkaline phosphatase >260 units/l	Heart disease
White cell count $>10\times10^9$/l	Alanine transaminase >100 units/l	Chronic lung disease
Creatinine $>130\,\mu$mol/l	Temperature >38°C	Steroid R_x
Albumin <30 g/l	Age >60 years	
	Diabetes mellitus	

significance of the difference between groups was ascertained by the log rank test. Deaths unrelated to cancer were treated as censored data. A series of Cox proportional hazard models using various baseline factors as covariates were developed in order to determine independently significant long-term survivor functions. Statistical significance was taken as $P<0·05$; values of marginal significance are stated where appropriate ($P=0·05–0·10$).

Results

There were 52 patients with ampullary adenocarcinoma with a median age of 69 years (range 30–91 years) of whom 28 were women (54 per cent). Important clinical features are summarized in *Table 2*.

Endoscopic diagnosis

Forty-five patients had side-viewing duodenoscopy and all were found to have the gross appearance of ampullary carcinoma. Endoscopic biopsies were diagnostic of carcinoma in 36 cases (80 per cent) and were equivocal in the remainder. Gallstones were found in nine of the 52 patients (17·3 per cent) either by ERCP or by laparotomy.

Treatment and complications

The type of treatment received is detailed in *Figure 1*, and the comparison of risk factor scores is shown in *Table 3*. Of the 38 patients who underwent laparotomy seven patients had planned pre-operative endoscopic drainage (ED) at a median of 21 days (range 12–35 days). An eighth patient, aged 80 years, also had successful ED as a definitive procedure but elected for a Whipple's operation 3 months later. One surgeon routinely performed wide local resection (four cases) but the preferred resection procedure of the other surgeons was a Whipple's operation (24 cases). In the absence of distant secondaries resectability was determined by trial dissection of the neck of the pancreas from the superior mesenteric vein. Initially, patients over 70 years were not considered for major resection, but following the introduction of ED these patients were, provided they did not have any major medical risk factors. Thus five patients over 70 years had a Whipple's resection, four of whom survived.

Table 2 *Important clinical features of 52 patients with ampullary carcinoma*

Clinical feature	Patients *n*	Patients Percentage
Jaundice	42	81
Progressive	40	77
Intermittent	2	4
Anorexia/weight loss	40	77
Pruritus	22	42
Abdominal pain	25	48
Epigastric pain	11	21
Right hypochondrial pain	12	23
Back pain	2	4
Related to eating	2	4
Palpable gallbladder	21	40
Nausea/vomiting	17	33
Rigors	12	23
Anaemia/GI bleeding	5	10
Diabetes		
Recent onset	3	6 (2 weeks–5 months)
Long-standing	3	6 (5–25 years)
Acute pancreatitis	3	6
Abdominal mass	1	2
Duration of symptoms (months)	Median 2	Range 0·3–16

The median serum bilirubin level in the ten patients with unresectable tumours who underwent a surgical bypass was 309 μmol/l (range 42–554 μmol/l), compared with 109 μmol/l (6–514 μmol/l) in those who had a Whipple's resection ($P=0·0027$). The median major risk factor score was zero (range 0–4) for resection cases compared with a median score of one (0–5) for the bypass group ($P=0·052$). Eight of the patients in the bypass group underwent surgery before the routine availability of ED; one of the remaining two patients had pre-operative ED but was found to have an inoperable tumour at laparotomy.

Major complications and/or death occurred in 17 of the patients undergoing surgery (*Table 4*). Eight patients had wound infections (positive culture in six cases) and this was an isolated complication in three patients. The median age of patients without complications was 63 years (range 52–83 years) compared with a median age of 70 years (53–80 years) in those with major complications ($P=0·0106$). The median total risk factor score was 3 (range 0–8) for those not developing complications and 4 (2–9) for those who did ($P=0·0540$). For Whipple's resection alone age was again the only factor which was significantly different between those who had an uneventful postoperative course (median 62 years, range 52–78 years) and those who developed complications (median 68 years, range 61–80 years; $P=0·0326$). There was no difference in

Table 3 *Comparison of risk factors between patients having surgical procedures and patients having endoscopic drainage*

	Surgical procedures (*n*=38)	Endoscopic drainage (*n*=13)	*P*
Age (years)	67 (52–83)	82 (69–91)	0·0001
Haemoglobin (g/dl)	12·0 (8·9–14·8)	10·5 (7·8–13·9)	0·0202
Haematocrit (%)	36·8 (27·0–46·3)	32·1 (24·9–41·0)	0·0185
Albumin (g/l)	36 (26–44)	30 (20–40)	0·0144
Major risk factors	0 (0–5)	2 (0–5)	0·0059
Minor risk factors	3 (0–5)	3 (2–5)	n.s.
Medical risk factors	0 (0–3)	1 (0–2)	n.s.
Total risk factors	4 (0–9)	6 (3–9)	0·0018

Values shown are median (range). Only significance differences are shown. N.s., not significant. Other variables including blood white cell count, serum urea, creatinine, total proteins, bilirubin and liver enzymes were not significantly different

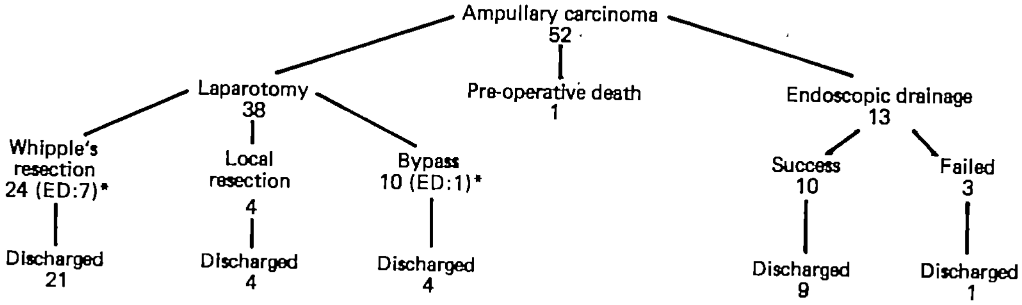

Figure 1 *Treatment in all 52 patients with ampullary carcinoma. *ED, pre-operative endoscopic drainage*

terms of postoperative outcome between those who had preoperative ED and those who did not. All surgical procedures were performed by consultant staff or senior registrars advanced in training. Postoperative complications were unrelated either to the grade of surgeon or to any individual.

Endoscopic drainage was achieved in 10 of the 13 patients in whom this was attempted as a definitive procedure. An endoprosthesis was inserted in one patient in whom the sphincterotomy was considered to be inadequate. In two other patients in whom the CBD could not be cannulated, endoscopic needle knife choledochoduodenostomy was performed. ED was not performed in three patients, in one because of a Polya gastrectomy and in another because of a very large tumour; in the fixed case, failure occurred during the very early experience with these techniques. Two of these patients and one other who had successful ED died in hospital at 4, 14 and 11 days respectively from debility. The remaining patient who had a failed ED died 6 weeks following hospital discharge. The group of patients selected for ED as definitive treatment had more risk factors compared with those undergoing surgery (*Table 3*). Overall ED was successful in 17 out of 21 patients (81 per cent). There were no immediate complications attributable to any of the endoscopic drainage procedures.

Table 4 *Major complications occurring in 38 patients undergoing surgery*

Complication	Whipple's resection ($n=24$)	Local resection ($n=4$)	Bypass procedures ($n=10$)
Pancreatic fistula	6	0	0
Biliary fistula	0	0	2
Intra-abdominal abscess	2	1	0
Acute cholangitis	0	0	2
Haemorrhagic pancreatitis	1	0	0
Septicaemia	2	0	1
Severe chest infection	4	2	1
Haemorrhage	3	2	2
Hepatorenal syndrome	1	0	4
Number with complications	9 (37·5%)	2	5
Number of deaths	3 (12·5%)	0	6*

* One patient without overt complications died at 27 days from general debility.

One patient aged 30 years died from acute cholangitis (blood cultures grew *Streptococcus faecalis* and *Streptococcus pneumoniae*) before ED was available. Endoscopic biopsies were equivocal for adenocarcinoma and the patient died before surgery was undertaken—the diagnosis was confirmed at post mortem.

Histopathology

A diagnosis of ampullary adenocarcinoma was obtained in 50 patients: in 34 patients by tissue obtained at laparotomy, in 15 by endoscopic biopsies alone and at post mortem in one patient. Two elderly patients had endoscopic biopsies which were equivocal for carcinoma but both died from progressive malignancy.

Long-term follow-up

The estimated 5 year survival rate following hospital discharge for the 24 patients who had resection was 55·9 per cent compared with 13·3 per cent for those who had palliative procedures ($\chi^2=10{\cdot}02$, d.f. = 1; $P<0{\cdot}001$) (*Figure 2*). For resection cases long-term survival was independently related to the grade of tumour differentiation ($P=0{\cdot}003$) and stage ($P=0{\cdot}006$). No other single factor (including age, sex, length of history and weight loss) was significantly correlated with long-term survival. Age was a significant factor by univariate analysis ($P=0{\cdot}032$) but not significant by multivariate analysis.

Discussion

The median age of patients was at least 10 years greater than that reported from North American series[4,6–8,12] and reflects our inclusion of all patients with ampullary carcinoma. Obstructive jaundice was the presenting feature in the great majority of cases but in contrast to other series fluctuating jaundice was unusual[18,28]. Symptoms such as right hypochondrial or epigastric pain, rigors and acute pancreatitis were more indicative of gallstones which were found in 17 per cent. Reliance on ultrasound alone in patients with such symptoms would be inadequate for diagnosis and emphasizes the importance of endoscopy. In jaundiced patients important clinical clues to the correct diagnosis included a history of anaemia or gastrointestinal bleeding.

The introduction of duodenoscopy to Leicester has had an important impact on diagnosis. The incidence of ampullary carcinoma rose from eight cases in the first 4 years before the introduction of ERCP to 44 cases in the next 9 years. During the

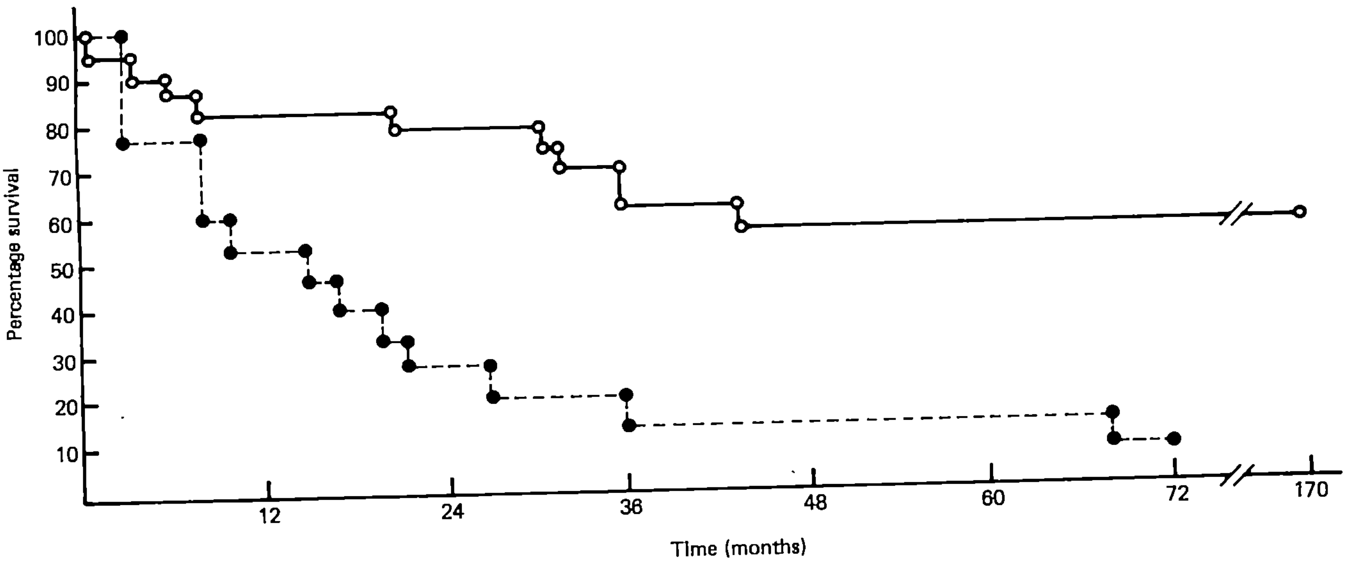

Figure 2 *Life-table survival curves following resection* (○, n = *25*) (*Whipple's operation, 21; local resection,* 4) *and successful palliative bypass procedures* (●, n = *13*) (*operative bypass, 4; endoscopic drainage, 9*). $P<0{\cdot}001, \chi^2=10$, *d.f.* = *1*

latter period this represented approximately one new case per 175 000 population per year, which is more than double that reported from Bristol,[18] where the rate of duodenoscopy has been lower. This change appears to reflect an increase in the referral of patients both for diagnostic ERCP and for endoscopic treatment of obstructive jaundice in elderly patients. The value of endoscopy also lies in obtaining a histological diagnosis before surgery to differentiate neoplasia from inflammatory pseudotumours of the ampulla[29].

The major complication rate of Whipple's resection was 38 per cent and is comparable to rates of 42–62 per cent reported elsewhere[6,7,9,30]. The mortality rate of 12·5 per cent is also similar to that reported from several other centres, including some with an expressed specialist interest[1,6–9,11]. The importance of surgical expertise has been shown by the unit from Manheim with a mortality of only 3 per cent following 33 Whipple's resections[5]. Although age was an important factor affecting the major complication rate we would agree with Kairaluoma *et al.*[11] that 70 years should not be regarded as the upper age limit for performing a Whipple's resection as proposed by some authors[1,31]. Pre-operative endoscopic drainage (ED) has been adopted recently in Leicester as a routine. This approach not only allows an improvement in liver function and nutrition[32] but also permits a more accurate histological diagnosis on subsequent biopsies if the initial biopsy was not diagnostic of carcinoma[29]. Unlike percutaneous transhepatic external biliary drainage[33] ED is not associated with any significant complications[27,32].

Local resection of ampullary tumours has recently been proposed as an alternative approach to a Whipple's operation[20,21]. Although a nil mortality rate has been reported for local resection from the Manchester region[20] the mortality for 56 cases collected from the recent literature was 14·3 per cent[4,9,12,13,21,34].

Ten patients with inoperable lesions had surgical bypass with four of the six resultant deaths due to the hepatorenal syndrome. The median bilirubin in the bypass group was three times higher than that in the resection group and indicates the relevance of deep jaundice as a major factor in causing postoperative renal failure[35]. Eight of these patients were operated on before the introduction of ED and would have probably benefited from pre-operative biliary drainage.

Three out of 13 patients treated by ED as definitive treatment died in hospital, but none of these was considered a surgical candidate. Patients in this group were significantly older and had greater risk factor scores than those undergoing surgery. The overall initial success rate of ED was 81 per cent and is similar to that reported by others[27,32,36]. In only one case was it necessary to use an endoprosthesis and unlike others we do not consider it necessary to use this routinely[36].

This study has shown the importance of using risk factor scores to compare immediate outcome in relation to treatment. Although major operative complications were related to the total risk factor score and to age in particular we do not believe that they should be used alone to judge the feasibility of undertaking surgery in individual cases.

In recent years an improvement in the 5 year survival rate has been reported following a Whipple's resection[5,11,15,16] but the results are highly variable ranging from 6 per cent reported from Japan[3] to 50–62 per cent reported from Europe and North America[5,15,16]. We have shown that long-term survival was independently correlated with tumour grade and the new staging system. Adoption of such a histopathological classification may provide for an objective comparison of survival from different series, not only following a Whipple's resection but also following local resection. Whereas Knox and Kingston recently reported a 5 year survival rate of more than 50 per cent for local resection, the experience of others indicates a much lower long-term survival[4,34,37]. The case for local resection has yet to be made and supporters of this approach should include precise histological analysis in future studies. As recently discussed by Trede[38] we would also reject the idea that regional pancreatectomy is the best curative procedure[39].

In conclusion, patients with ampullary tumours should undergo endoscopic biopsy and drainage. Endoscopic drainage is the preferred method of treating patients considered to be at high risk from surgery. The Whipple's operation remains the treatment of choice for resectable tumours, but must be undertaken by surgeons with the necessary skill. The new staging system may prove to be valuable in assessing survival in future studies.

Acknowledgements

We are deeply indebted to the consultant surgeons and general practitioners who allowed us to report on their patients and provided vital follow-up data. We thank Mrs R. Aldwinckle for secretarial assistance.

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Correspondence

Bacterial growth kinesis in generalized peritonitis

Sir

With reference to the recent paper by Krukowski *et al.* (*Br J Surg* 1987; **74**: 303–6) we see a further demonstration of how easy it can be to produce scientific data which are clinically misleading. Since the technique of lavage used in their study was no doubt performed thoroughly, this must result in lavage solution, peritoneal exudate and abdominal pathogens reasonably homogeneously mixed.

Therefore, would it not be the case that a sample of residual peritoneal fluid taken immediately after lavage will consist largely of the lavage solution itself? In other words, what has been achieved is a clinical '*in vivo*' inoculum mixed with the lavage solutions under test, so only really measuring the ability of that lavage solution to sustain or inhibit bacterial growth. I suggest it is difficult to draw any meaningful conclusions from the bacterial growth rates without data on the antibiotic concentrations of the sample.

The authors, however, do make a very important point that there is a lack of prospective controlled trials in severe generalized peritonitis. Indeed, even antibiotic prescribing for generalized peritonitis is based largely on evidence with their use in routine elective surgery.

Peritonitis, especially of faecal origin, has remained a complex problem. The work of Filler and Sleeman[1,2], however, demonstrates the principal factor for mortality and morbidity is due to residual abdominal sepsis and continued production and absorption of endotoxins in the already compromised patient. There can be little doubt that intraperitoneal antibacterial therapy is of fundamental importance in eradicating this problem.

Prospective controlled trials in peritonitis are difficult to perform and ethical considerations make such studies virtually impossible for established drugs. There are, however, several such controlled studies and supportive evidence for a new drug, Taurolin® (taurolidine)[3–14]. This may be of interest to those seeking such a therapy.

When designing appropriate antibacterial therapy for the treatment of established peritonitis, the choice should be based on evidence of a drug's efficacy in this clinical indication itself. Due to the complex pathology encountered, much more consideration should be given to the role of endotoxins and their effect on patient prognosis.

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Authors' reply

Sir

Thank you for the opportunity to reply to Mr Stebbings. Our data are not clinically misleading. Our observations are that a high topical concentration of antibiotic has a more certain action at the time of laparotomy than conventional systemic antibiotics even when supplemented by saline lavage. The increased activity of antibiotics at high concentration is well documented and advocacy of a topical antiseptic must be based on exactly the same premise.

Evidence that we have not been clinically misled by the use of tetracycline lavage is well known[1]. Updated experience with an antibiotic policy based on tetracycline lavage during the 10 years to December 1986 in 389 patients with severe peritoneal sepsis was associated with a mortality of less than 7 per cent (the mortality due to uncontrolled sepsis being 3·1 per cent) and a wound infection rate of 8 per cent.

Since the first clinical reports on taurolidine appeared more than 10 years ago it remains generally unobtainable and unlisted in either MIMS or the British National Formulary. It depends, like noxythiolin, on the release of formaldehyde for its antibacterial action and, on the evidence available, appears to be as effective or ineffective.

We agree that intraperitoneal antibacterial therapy is important in the eradication of peritoneal infection and we have been consistent exponents of this form of therapy with antibiotic lavage. Stebbings claims that there have been several controlled studies using taurolidine but most of the studies to which he refers are not controlled trials. The wound sepsis rates in 'dirty' operations of 20–46 per cent[2,3] and a mortality of over 20 per cent in the largest series[4] are not convincing evidence of a dramatic 'new' therapeutic agent.

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Nissen fundoplication and pyloroplasty in the management of gastro-oesophageal reflux in children

Sir

It is unfortunate that Mr Davidson and his colleagues have drawn the conclusion that serious complications are common after Nissen fundoplication for intractable gastro-oesophageal reflux (*Br J Surg*

1987; 74: 488–90). Their conclusion that pyloroplasty should be added to prevent gas bloat is just as unfortunate and will not, I hope, be adopted by the majority of surgeons.

Gastro-oesophageal reflux is uncommon in childhood, but is extremely common in adult life. The bulk of helpful literature therefore concerns adults, but the authors seem to have a limited outlook in the library. Fifteen of their twenty references are from the paediatric literature, and they ignore the most useful contribution in recent years, namely the concept of the floppy Nissen. This was introduced more than 10 years ago by the Chicago group to avoid the problem of bloat. Since then many hundreds of these operations have been done and reported in the literature as having a low incidence of complications. My own experience is of more than 200 operations with a 0·5 per cent incidence of prolonged bloat. My paediatric colleagues in Manchester have had a similarly satisfactory experience.

A small retrospective study of 20 children is no basis on which to suggest an additional operative manoeuvre which may itself produce long-term complications. One could just as easily support the contention that all reflux surgery should be done by experienced gastroenterological surgeons and not by paediatric surgeons.

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Authors' reply

Sir

We cannot accept Mr Bancewicz's statement that gastro-oesophageal reflux is uncommon in children. It is a common paediatric problem, particularly in infants and the mentally and physically handicapped. Few, however, require surgical intervention and hence the operative procedure of choice remains controversial.

Reviews of antireflux surgery in adults are not necessarily comparable to those of children. For example, physical handicap is a major aetiological factor in the latter, comprising 40 per cent of our series. This would explain our bias towards the paediatric literature.

Complication rates of 20 per cent after antireflux surgery in children have been reported in major series from both Britain[1] and the USA[2].

Gas-bloating, a major cause of postoperative morbidity, has not been encountered in a series of 267 children undergoing Nissen fundoplication with pyloroplasty[3]. Although we are unaware of any long-term complications of carrying out pyloroplasty in children, or indeed of the comparable procedure of pyloromyotomy, we remain concerned about such a possibility. The absence of bloat in our series was an observation rather than a dogmatic statement of cause and effect. The operative technique we used was comparable to the 'floppy Nissen' which has been well documented in adults, however the efficacy of this procedure alone in children remains to be established. If indeed a 'floppy Nissen' alone proves to be effective in preventing gastro-oesophageal reflux and gas-bloating in children, then we would agree that a pyloroplasty is avoidable.

As far as the concept of specialized paediatric surgery being carried out by general surgeons is concerned, we would expect that a few would agree to this being a major advance.

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Reflux stricture of the oesophagus

Sir

There is one serious omission from the otherwise excellent review of reflux stricture of the oesophagus by Watson (*Br J Surg* 1987; 74: 443–8).

No mention is made of the Angelchik antireflux prosthesis in the surgical management of oesophageal reflux and stricturing. While we endorse the general medical and endoscopic management policies described by Watson, we feel it important to draw attention to the fact that there is now established evidence that the Angelchik prosthesis is at least as good as other antireflux procedures in controlling oesophageal reflux[1] and strictures[2]. Insertion of the Angelchik prosthesis requires minimal abdominal interference and therefore its use is attractive especially in the elderly and high-risk patients.

A recent audit of the UK experience of the Angelchik prosthesis reveals that of the order of 5 per cent are eventually removed operatively[3]. This failure rate compares favourably with the more traditional antireflux surgical procedures.

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Author's reply

Sir

I would like to thank Messrs Dawes, Deutscher and Gear for their comments. The purpose of my article was to highlight the various therapeutic strategies in the management of reflux stricture, and not to present an exhaustive list of the various types of antireflux procedure. As the review was based on a large personal series, I considered it appropriate to describe the antireflux procedure used in the management of these patients, but the question of the relative merits of the various antireflux procedures will be addressed in a forthcoming publication.

However, the points raised by the authors require comment, as the use of the Angelchik prosthesis is controversial. Two recently published prospective studies[1,2] have reported postoperative dysphagia in up to 30 per cent of patients after prosthetic insertion, and mechanical problems requiring removal of the prosthesis in 11 and 17 per cent of patients respectively. As to the cited reports of its efficacy in reflux control, these rely heavily on symptomatic and radiological parameters; some find difficulty in reconciling a 96 per cent efficacy on Visick grading with a prosthesis removal rate of 11 per cent[3].

The debate on the relative efficacy of the various antireflux procedures will continue, but in 1987 the assessment of results should be based on objective reflux control demonstrated by endoscopy, biopsy and pH monitoring and not on symptoms, radiology and how few re-operations are required for complications of the procedure.

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Sex hormones in carcinoma of the exocrine pancreas

Sir

We were most interested to read your leading article this month (*Br J Surg* 1987; 74: 441–2) concerning the possible role of sex hormones in carcinoma of the exocrine pancreas.

Mr Greenway was kind enough to mention the Leeds based clinical trial of tamoxifen in unresectable pancreatic adenocarcinoma. In fact, this regional trial has been running since February 1987 and we are planning to recruit for 2 years. We would be very pleased to send a protocol to anyone who might be interested.

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Hyperalimentation of jaundiced patients during percutaneous transhepatic biliary drainage

Sir

We read with interest the article by Foschi *et al.* (*Br J Surg* 1986; **73**: 716–19) which suggested that patients with obstructive jaundice may benefit from the use of hyperalimentation during percutaneous transhepatic biliary drainage (PTBD). Several points require comment.

Firstly, as the authors pointed out, the presence of malignant disease is an important risk factor. Seventeen patients (almost one-third of those in the study) had benign conditions and were included in the final analysis. Few authors would now recommend routine PTBD for patients with benign disease, and it is important to separate the difference in the complication rates for this group and for the malignant group. Moreover, no information is provided comparing the severity of nutritional defects between patients with benign and malignant disease, or between the groups with and without hyperalimentation.

Part of the rationale for the study was based on the idea that renal function in these patients is impaired at the time of operation. No information on this is provided either at the beginning or at the end of the drainage period. McPherson *et al.*[1] found that, with correction of dehydration and electrolyte imbalance (much less hazardous than PTBD), normal renal function could be restored given at appropriate time. It may be that the results of hyperalimentation seen in the present study could also be achieved without PTBD.

The authors only compare, statistically, overall complications between the two groups and it seems unlikely from their data that the incidence of severe complications was reduced by hyperalimentation. Certainly the rate of infective complications is not less (4/28 *versus* 9/32, $\chi^2 = 0{\cdot}97$, $P = 0{\cdot}32$). Indeed, the reduction of mortality cited in the text and in the abstract does not reach statistical significance (4/32 *versus* 1/28, $P = 0{\cdot}22$, Fisher's exact test).

Much of the literature on jaundice and biliary drainage reveals problems with planning and evaluation of trials which in themselves have laudable aims. Unfortunately this trial, whose results remain unproven, may only have added more mud to those cloudy waters.

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Authors' reply

Sir

The message of our paper was that hyperalimentation of patients on percutaneous biliary drainage improves the results of surgery for obstructive jaundice. Dr Halliday raises objections which are related to biliary drainage rather than to hyperalimentation. We maintain that Dr Halliday's criticisms do not invalidate our conclusions for the following reasons.

Patients with benign conditions were at increased risk for complications because they had serum bilirubin > 200 μmol/l (reference 1). Even if they were subjected to a lower risk of complications, it would be equally distributed between the two groups of treatment. Moreover, the rationale for use of hyperalimentation is that obstructive jaundice can cause malnutrition also in patients with benign conditions; it was not our aim to compare the effects of hyperalimentation in benign and malignant conditions, and we believe it was correct to consider all the patients with deep jaundice.

We apologize for not having given details of the incidence of malnutrition in the two groups of treatment; however we specified that the two groups of treatment had the same clinical characteristics, which include the incidence of malnutrition and the impairment of renal function.

No part of the rationale for the use of hyperalimentation includes any influence on renal function; hyperalimentation did not influence the incidence of renal failure. As for the effects of PTBD on renal function: first, we studied two groups, one treated with PTBD, the other one with PTBD plus hyperalimentation; second, all the patients had an appropriate pre- and perioperative treatment to prevent renal failure. Both these conditions make it impossible to assess the effect of PTBD on renal function.

We were delighted by Dr Halliday's hypothesis that patients with obstructive jaundice could benefit from hyperalimentation without biliary drainage. However, it is well known that during obstructive jaundice there is a severe metabolic derangement, with impairment of protein synthesis, gluconeogenesis and ketogenesis[2]; we do not believe hyperalimentation can be of any benefit when the liver cannot metabolize the substances which are administered. PTBD, by improving liver function, makes hyperalimentation possible.

We cannot agree with Dr Halliday who considers anastomotic leakage, acute renal failure and hepatic failure (which caused four deaths in our series) to be minor complications. If they are included with infective complications, as was done by the Hammersmith group in a previous paper[3], a significant reduction of the complication rate can be demonstrated with hyperalimentation. As a matter of fact, both in the abstract and in the discussion we concluded that hyperalimentation plus PTBD 'can reduce the rate of complications' and 'can improve the prognosis after the operation'.

Finally, we would like to quote the following sentence extracted from an article of Dr Jeppsson and Halliday[1] 'It has been shown that (during malignant obstructive jaundice) if sepsis can be avoided, vigorous nutritional therapy can improve the nutritional status.... All but 1 of the patients with sterile bile improved their pre-albumin levels during drainage and had fewer postoperative complications'.

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Mechanical bowel preparation for colonic resection and anastomosis

Sir

I read with interest the article by Irving and Scrimgeour (*Br J Surg* 1987; **74**: 580–1) and editorial comment of Johnston (*Br J Surg* 1987; **74**: 553–4). At the 1976 Spring meeting of the Surgical Club of South West England I presented 48 consecutive elective colonic resections without mechanical bowel preparation and antibiotic cover in the form of ampicillin alone. No protecting colostomies were performed. My results were as good as contemporary figures from other centres with a wound infection rate of 16·6 per cent, anastomotic leak in only one which closed spontaneously and a mortality of 4·2 per cent, both from myocardial infarction in 80-year-olds. Since that time I have continued without bowel preparation but have added metronidazole to the antibiotics; wound infection is now at 5·8 per cent and anastomotic leak a rarity.

I therefore agree with Irving and Scrimgeour that bowel preparation is not necessary and possibly harmful. I dispute Johnston's explanation of the results as my methods vary in all respects with Irving. I use a double layer of continuous catgut for the anastomosis, always use a suction drain, suture the wound in layers using Dexon® for the abdomen and subcuticular for the skin, and perform an anal dilatation at the end of the operation. May I add, the large bowel is designed to carry faeces, it is certainly not designed to carry soap and water, mannitol and various other preparations used in an often unsuccessful attempt to cleanse it.

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Fine needle aspiration cytology of soft tissue tumours

Sir

We have read the recent article by Kissin *et al.* (*Br J Surg* 1987; **74**: 479–80) with interest and considerable concern. They claim that fine needle aspiration of soft tissue tumours provides an overall diagnostic accuracy (benign *versus* malignant) and predictive value of a positive diagnosis of over 90 per cent. They, therefore, claim that this technique may be a useful adjunct in planning the surgical management of these lesions.

The true value of their findings is, however, very questionable. They admit that, in order to minimize sampling error, aspirates were taken from excised specimens, not from the patient pre-operatively. This arrangement bears no comparison to the 'real' surgical patient, in whom sampling error is a major and well-recognized problem. Furthermore, despite adopting what should have been an optimal technique, they admit that 'about 20 per cent' of the smears were inadequate for diagnostic purposes. In fact, from their figures, 30 per cent appears a more accurate figure. In other words, almost one in three aspirates failed even when taken in a laboratory. For reasons which are unclear, this substantial group of cases were then excluded from the calculation of results.

A further very worrying problem is that, out of 18 smears reported as benign by the 2 cytologists, 10 proved to be malignant tumours. Clearly, if these had been *in vivo* results, they would have been detrimental in planning treatment.

It is important to note that these smears were interpreted by 'enthusiasts'. These neoplasms are relatively rare and are recognized to be a difficult area of histopathology. One must, therefore, be concerned about the accuracy that might be obtained in a non-specialist laboratory.

We would strongly deprecate the widespread use of fine needle aspirations for the diagnosis of soft tissue tumours, principally because of the dangers of sampling error (both anatomically and within a given tumour) and of inevitable cytological inexpertise in this field. We believe that, in this specific context, the technique should only be applied and interpreted in specialist centres dealing with a minimum of 250 soft tissue tumour aspirates per annum. Only then is there any hope of obtaining reliable diagnoses.

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Authors' reply

Sir

We understand the caution of Fletcher and Young, but the use of fine needle aspiration biopsy (FNAB) in the diagnosis of soft tissue tumours is not without precedent. In our preliminary study the inadequate smear rate is high (a more careful reading shows this to be 22·2 per cent and not 'almost one in three') and relates solely to the aspiration technique. Such a problem is also encountered in FNAB of the breast (41·6 per cent)[1] and thyroid (21 per cent)[2]. One lesson we have learned is that the 'intact patient' is a better subject than the excised specimen, especially as in the patient the problem of inadequate smears is almost eradicated by repeating the procedure[2].

The false negative rate results from reluctance of experienced soft tissue diagnosticians to over-diagnose sarcoma on borderline smears (note that we did not use a 'suspicious' category). We stress the very much lower false positive rate which has much greater import.

It is assumed that the cytology of soft tissue lesions is relatively undiscovered, but detailed reports are available. Dr Fletcher and Mr Young are referred to Willems[3] and the comprehensive references quoted by him. Expertise will only improve with experience and, modest though this series is, its clinical advantages are in our view worthy of development.

We would wish to know where the figure of 250 soft tissue tumour aspirates per annum is plucked from. Of 800 soft tissue sarcomas registered annually in England and Wales, 60 new cases provide fresh tissue at the Royal Marsden Hospital and are studied in a prospective fashion. Unfortunately there is no centre in the world that deals with 250 soft tissue aspirates per annum. Åkerman *et al.*[4] (Lund) reported 178 cases in 5 years (24 per cent sarcomas), whereas Layfield *et al.*[5] (UCLA) collected 136 cases in 4 years (38 per cent sarcomas). For comparison, we aspirated 54 tumours in 1 year (89 per cent sarcomas). Though we cannot accept that only very large specialist centres should use FNAB, we recommend that soft tissue tumours should be managed by surgeons and pathologists with a dedicated interest in the field. One has to collect material as it is available, preferably by collaborative series, examine it and employ the cytodiagnoses with clinical wisdom as part of the standard investigations—only then will reliability be acquired

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1. Patel J, Gartell PC, Smallwood JA *et al.* Fine needle aspiration cytology of breast masses: an evaluation of its accuracy and reasons for diagnostic failure. *Ann Roy Coll Surg Engl* 1987; **69**: 156–9.
2. Anderson JB, Webb AJ. Fine-needle aspiration biopsy and the diagnosis of thyroid cancer. *Br J Surg* 1987; **74**: 292–6.
3. Willems J-S. Aspiration biopsy cytology of soft tissue tumours. In: Linsk JA, Franzén S, eds. *Clinical Aspiration Cytology*. Philadelphia: JB Lippincott, 1983: 319–47.
4. Åkerman M, Idvall I, Rydholm A. Cytodiagnosis of soft tissue tumours and tumour-like conditions by means of fine needle aspiration biopsy. *Arch Orthop Traumat Surg* 1980; **96**: 61–7.
5. Layfield LJ, Anders KH, Glasgow BJ, Mirra JM. Fine needle aspiration of primary soft-tissue lesions. *Arch Pathol Lab Med* 1986; **110**: 420–4.

Postsplenectomy infection

Sir

We have read with great interest the Review by Cataldo, Puleo, Li Destri *et al.* (*Br J Surg* 1987; 74: 343–5) examining the incidence of overwhelming postsplenectomy infection (OPSI) in patients who have undergone splenectomy after trauma. The authors suggest that the choice of surgical alternatives to splenectomy is confused, due mainly to inability to define the precise incidence of OPSI after splenectomy for trauma. They suggest that further retrospective and prospective studies on large groups of patients should be carried out before an 'ideal' operation can be recommended.

As they indicate, incidence of OPSI in patients splenectomized after trauma (particularly adults) is very low, and we believe its incidence is likely to become lower still. This is because postsplenectomy patients should routinely receive immunization against the most common causative organisms of OPSI, and numbers of patients are prescribed prophylactic penicillin for long postoperative periods. As well as this, OPSI is now a well-recognized syndrome and patients should be advised of the importance of seeking medical advice early after the onset of non-specific symptoms which may precede OPSI. Clinicians too are now more aware of OPSI in this group of patients and it is hoped that the condition is more likely to be diagnosed and treated vigorously. These factors are likely to greatly increase the difficulty of the suggested statistical studies of alternative surgical treatments to splenectomy.

An alternative approach, which should yield data predictive of the value of the treatment, is to monitor immunological parameters in patients treated with different regimens. The most likely explanation for OPSI is that splenectomized patients mount a slower and lower antibody response to infections. This diminished response is critical when the organism can multiply rapidly and overwhelm the host before an effective response is mounted by the immune system. This diminished response is compounded by the fact that the spleen is the organ which is primarily responsible for the phagocytosis of bacteria opsonized with low concentrations of antibody.

Therefore, we suggest that studies on alternative treatments to splenectomy should include investigation of humoral and phagocytic immune functions *in vivo*, both of which are abnormal after splenectomy. The normalization of either of these arms of the host defence system is likely to be easier to detect, require fewer patients, and be reasonably predictive of the value of the treatment earlier than monitoring OPSI incidence.

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Book reviews

Principles and Practice of Research

H. Troidl, W. O. Spitzer, B. McPeek, D. S. Mulder and M. F. McKneally. 270 × 190 mm. Pp. 380 + xvii. Illustrated. 1986. Berlin: Springer-Verlag. DM 128.

Understanding of the wider aspects and responsibilities of medical research are prerequisites for those with an active or passive involvement in the scientific investigation of medicine. For those actively involved in medical research a text to guide them in designing, performing, analysing and presenting their studies should be available. For those passively involved, access to information about how studies can be performed, the pitfalls that could have been encountered and what the results might mean is necessary if a worthwhile evaluation of the research of others is to be undertaken. A book which seeks to meet these needs should not attempt to replace the invaluable advice available from experienced colleagues as their often distinctly individual approach is one of the safe-guards against scientific stagnation.

This book is a multi-author, multinationality work with five editors: two from each of Canada and the USA and one from Germany. There are 50 contributors from 9 different countries; over half (28) from Canada and the USA, 19 from Europe and 3 from Japan. This permits a wide spectrum of opinion which has been well controlled by the editors. The book has 6 sections with a total of 40 chapters, there are less than 400 pages and only 12 chapters have more than 10 pages. This helps to make it readable either from cover to cover or in selected parts.

The first section on 'The rationale of surgical research' (five chapters) deals with the history and philosophy of research and has chapters on the roles and development of the surgical investigator. The final chapter, 'Facilitating scholarship: creating the atmosphere, setting and teamwork for research', contains many relevant and often forgotten aspects of the enjoyment that is derived from working in association with others.

Section two deals with 'Starting the research process' (eight chapters) and covers review and critical appraisal of the literature, organization and end-points of clinical studies. The chapters: 'Statistics demystified' and 'Some things you should know about computers' are good. The complex and difficult area of ethics in surgical research is introduced effectively with an extensive reference section (80 references). The chapter 'Ten tips on preparing research proposals' is particularly valuable and laudable for its brevity.

Section three deals with 'Selected strategies of research' (eight chapters); in this section different types and aspects of research are described. It ranges from a lengthy description of the Marburg experiment as an example of the 'horizontal organization' of a whole department of experimental surgery and pathological biochemistry, to a short description of 'vertical organization' in the evolution of an individual research project. Chapters on animal experimentation, clinical research, multi-centre trials and health service research cover most of the necessary material; with the chapter on animal research being especially well written and pertinent. Squeezed in between 'Multi-centre trials' and 'Health service research' is a chapter with a rather deceptive title, 'Evaluation of the diagnostic process'. This is a must for clinical investigators as it elucidates the concepts of validity, sensitivity, specificity, utility, gold standards and independence, most of which are poorly understood and badly used. Finally, there is a chapter on non-experimental methods in which various epidemiological methods are described. It includes a discussion on 'association is not necessarily causation' a point too often forgotten by the enthusiastic collector of medical data.

Section four is entitled 'Reporting your work' (eight chapters). If any part of this book is to be singled out as the best or the most valuable, then the part of this section which deals with presentation of research is it. The chapters on 'Ten minute presentations', 'Longer talks', and 'Presenting at international meetings' should be read by all who have the opportunity to stand up and tell an audience about their work. Useful advice can be found on abstract preparation, poster sessions and audio-visual aids. Surprisingly there are only two chapters on writing, one on writing for publication the other on what to do when asked to write a chapter in a book; of course it may be that this particular area has been specifically omitted as there is an extensive and worthwhile literature already available on this topic. A particular omission, which may be more relevant to readers from the UK, is a complete lack of mention of thesis producton. A thesis represents a peak in a research worker's writing career and therefore should have had a place in this book.

Section five deals with 'International perspectives on surgical research' (ten chapters), a fascinating section with chapters from all the nations represented by the contributors. The individual chapter coming from the country of origin of the reader will be of value. Disappointingly the references from the chapter on the UK have been omitted. Useful comparative data on the common characteristics and 'distinctive diversity' of surgical research is to be found in the final chapter of this section.

Section six, 'Opportunities in surgical research' (one chapter) is beautifully written by one of the greatest surgical investigators, Francis D. Moore. It is a fitting finish to an excellent book.

This book should be presented to a surgeon on the day that he realizes that surgical research will play a major role in his future life. It can be read before research is commenced, during a research career or once active research has come to an end. The investment of nearly £50 is more than the often impoverished research worker should be expected to bear, but it is a small investment if considered part of the research project he is undertaking.

A. Sim

Surgery Annual 1987

L. M. Nyhus. 168 × 240 mm. Pp. 371. Illustrated. 1986. Connecticut: Appleton Century Crofts. $65.00.

The 1987 volume of 'Surgery Annual' contains 17 chapters which include comprehensive reviews of prophylaxis for thrombo-embolism, parathyroid surgery, diverticular disease and the conservative management of breast cancer. There are good chapters on duplex scanning in vascular surgery, shock wave therapy for renal stones and the use of lasers for palliation of bronchial and oesophageal tumours, although these are slightly dated by the inevitable delays in publication.

There is also much with which one would take issue. The chapter on splenorenal shunts is unashamedly anecdotal and the management of postcholecystectomy syndrome eventually boils down to a pancreatic sphincteroplasty. Arterial chemotherapy for colorectal liver metastases is compared with intravenous therapy but whether it prolongs survival is not discussed.

None of the chapters on the lower oesopahgus is particularly inspiring, but the account of oropharyngeal dysphagia is recommended to anyone who deals with the upper gastrointestinal tract but tends to forget dysfunction of the normal swallowing mechanism as a cause of dysphagia. Nearly all the chapters have an extensive bibliography and otherwise rather disappointing articles on aortic cross-clamping and prostaglandins in acute pancreatitis will stand as important reference sources.

At $65 (£39) I think that the library should keep up its subscription but there are only half-a-dozen chapters one could really recommend to a Fellowship candidate, and rather fewer to a specialist.

T. Bates

Practical Laparoscopy

G. Berci and A. Cuschieri. 157 × 238 mm. Pp. 182. Illustrated. 1986. Eastbourne: Bailliere Tindall. £19.50.

With the increasing acceptance by general surgeons of the value of laparoscopy, a simple book on the practical aspects of this technique is valuable. This book is clearly written and presented and contains a wealth of useful information. It systematically covers the equipment necessary and how to use it. The authors state that this is a book for the beginner, but like many books with this stated intention it is also of interest to the experienced user.

The line drawings are effective and the black and white photographs of equipment are good; the black and white photographs of operative techniques are rather cluttered and would have been considerably simplified if they had been taken without the teaching attachment and its attendant observer. An introductory text, such as this, might have been better served by a selection of single colour plates.

I have little doubt that, as more surgeons use laparoscopy and the more advanced techniques of 'interventional' laparoscopy come into regular use, this book will find a place on the shelves of many surgeons offices.

A. Sim

Patient Care in Pediatric Surgery

L. L. Leape. 130 × 215 mm. Pp. 448. Illustrated. 1987. Boston: Little, Brown. £24.95.

This is not so much a textbook as a multiple choice answer. Although the title emphasizes patient care, this topic forms only a small fraction of the information the book contains: 'Pediatric Surgery Condensed' would have been a more accurate title for there is a succinct description of virtually all the common paediatric surgical problems and step by step analysis of how to detect and deal with them. Operative technique is not discussed so the book, as the preface states, is directed towards junior medical staff and nurses. The publishers refer to it as a 'portable guide' but it is really too bulky for a genuine vade-mecum. It might have been better to split the book into two parts, one for the neonate and one for older children, so each would fit into a jacket pocket on either side.

The writing is brief, clear and easy to read and the vernacular is employed here and there to good effect: for example, 'snugging up' the gastrostomy tube to prevent leakage is descriptive and almost quaint. Criticism is mostly minor and in some instances perhaps due to international differences in practice. Because of the layout of the book there is some repetition, for example, respiratory distress receives almost identical mention in chapter 6, part I and chapter 10, part II. The X-rays are mostly poorly reproduced; *Figures 13.1*, *46.1* and *94.1* are particularly 'foggy' and contribute nothing. There is some confusion in the use of units of measurement between SI and metric indicating the American ambivalence in this area: a dose of KCl of 4 MEq/dl and a serum calcium value of 12 mg/dl are both mentioned. Continuous intravenous morphine infusion in the control of postoperative pain is not described, which is a pity when so much stress is rightly laid on fear and anxiety as important causes of distress; the regular 'needles' required for bolus morphine therapy are a major contribution in this respect.

The section on abdominal pain is especially good, but the comment that an error rate of 5 per cent in the diagnosis of appendicitis is 'customary' seems a little odd; perhaps 'acceptable' would have been a better word. Many congratulations for the statement that 'drainage of the peritoneal cavity is useless' but none for omitting to recommend metronidazole in the antibiotic cocktail in acute appendicitis.

Laparoscopy should have been mentioned as one of the valuable diagnostic methods in impalpable testis. Finally, an American author has had the courage to state that 'circumcision is not medically indicated in the absence of disease of the foreskin'.

This book is very good value and deserves a place on the shelf of every paediatric surgical ward sister's office for ready reference by junior medical staff and nurses. It is a pity that a neonatal section and an older childs section cannot be placed in the appropriate wards.

J. E. S. Scott

Basic Surgery, Third edition

H. C. Polk Jr, H. Harlan Stone and B. Gardner. 235 × 175 mm. Pp. 735 + xvi. Illustrated. 1987. Hemel Hempstead: Simon and Schuster. £32.05.

This book is one of the new generation of surgical text-books which are based on methods of presentation, rather than the anatomical systematic approach of the classical surgical tome. There is much to be said for this type of approach since it mimics real-life diagnosis and management of patients with surgical problems. The problem-based approach is rarely comprehensive and this book is no exception, neglecting large areas of surgical disease. Since it is aimed at undergraduates, this selective approach is undesirable unless a standard surgical text-book is used to fill in the gaps. In the present economic circumstances which beset our medical students it is unlikely that they will wish to buy two text-books if they can get by with one. Most of our students will purchase one of the shorter text-books of surgery and a book on clinical examination and physical signs. For those who like a problem orientated approach, there are at least two British text-books which are superior, in this reviewer's opinion, to 'Basic Surgery'. Individual chapters are very uneven in style and presentation, some contain good line diagrams while others have none. Algorithms are scattered irregularly throughout the book but are not produced in a single style and at least two are so poorly designed that they require a magnifying glass to decipher. Many of the management outlines are skimpy and incomplete with little discussion or alternative options; for example, in the treatment of Stage I carcinoma of the breast there is little discussion on alternatives to mastectomy. There is also minimal information in this chapter on the management of disseminated breast carcinoma. For these reasons I will not be recommending this book to our students and it is too 'basic' for the fellowship candidates or qualified surgeons.

K. Burnand

Endothelialization of Vascular Grafts

P. P. Zilla, R. D. Fasol and M. Deutsch. 174 × 244 mm. Pp. 248. Illustrated. 1986. Basel, Paris, London: S. Karger. £90.00.

To replace a human blood vessel, which has been developed over 25 000 years of evolution, by a piece of cloth tubing and expect it to function for a useful length of time seems ambitious. What is interesting is not how often these grafts fail but that they ever succeed. In the aorto-iliac segment, where pressure, resistance and flow are reasonably constant, there is no great problem. In the distal arteries it is acknowledged that biosubstitutes, such as saphenous vein, provide the best material, but this is not always available. Research into failure of synthetic grafts has mainly concentrated on compliance because pulsatility is an important determinant in the behaviour of the distal circulation. Much effort has been made to develop a totally compliant prosthesis, but surgeons have recognized that, whatever the original nature of the implant, it becomes encased in fibrous tissue and within a few months is as rigid as a metal or plastic tube. Compliance, therefore, cannot be the answer. More recently, attention has been directed to the development of a biocompatible lining, and hence the motivation for this book, which reports a workshop on vascular surgery held in Vienna in 1986. The number of groups involved in research into endothelialization of artificial arteries is limited, and the field is very specialized. It could be covered in a 'state of the art' review article but, clearly, a hardback book has more commercial appeal. The problem here is one of overlap, so that every chapter rehearses the background to the problem. There is much useful information for the super-specialist, particularly in the chapters by Thompson and by Franke on cell-culture, and that by Zilla on shear-rates. The basic science is well presented though at unnecessary length. However, the clinical trials reported are too preliminary to be helpful as the number of patients is very small and the follow-up period too short to allow any valid conclusion. In spite of a statistical negative, some authors discuss a 'trend' in favour of the seeded group; this is not really justified.

All vascular surgeons await the development of an arterial prosthesis which performs as well as a vein. We are, at present, a long way away from this, and endothelial seeding is one of several possible new ways forward. The subject merits a review article in an international journal, but a hardback book at this enormous price could only be justified by more vigorous editing of the workshop's proceedings than has been achieved here.

A. Marston

Bladder Reconstruction and Continent Urinary Diversion

L. R. King, A. R. Stone and G. D. Webster. 255 × 180 mm. Pp. 379 + xxi. Illustrated. 1987. London: Wolfe Medical Publications Ltd. £62.00.

Various aspects of bladder reconstruction and continent diversion are most comprehensively considered with chapters from authors in the USA and Europe. The introductory chapters provide an account of the problems related to conduit diversion in children followed by a fascinating account of the historical development of reconstructive surgery. These set the scene for the five main sections: ureteric replacement, bladder augmentation and substitution, diversion, continent diversion and intestinal substitutes for the whole bladder. Most of the chapters give detailed accounts of surgical technique but they are very much 'what I do and how I do it' and, although there are exceptions, there is a relative scarcity of the long-term results of these difficult techniques. Perhaps the editorial pen could have been used with a little more effect to reduce unnecessary repetition in various chapters. These are minor criticisms for what really is an excellent book and essential reading for anyone involved with bladder reconstruction and related problems.

D. G. Thomas

Microbes and Human Carcinogenesis

M. J. Hill. 240 × 160 mm. Pp. 162. Illustrated. 1986. London: Edward Arnold. £25.00.

The theme that unites this short book—an infective aetiology for cancer—is reviewed clearly and logically. After an introduction to the mechanisms of carcinogenesis, separate chapters follow carefully arguing the case for and against microbial involvement in neoplastic transformation at different sites, not only in the areas of Dr Hill's well-known expertise—the colon and stomach—but also elsewhere e.g. liver, breast, bladder. Although the book can be enjoyed and understood by a general audience, there is also useful information for the specialist as well as an extensive and up-to-date reference list.

G. V. N. Appleton

Notices and announcements

18–24 October 1987
Recent Advances in Pancreaticobiliary Surgery
Glasgow, UK
Information: Professor D. C. Carter, University Department of Surgery, Queen Elizabeth Building, Royal Infirmary, Glasgow G31 2ER, UK

22–23 October 1987
First British Symposium on Surgical Stapling
Manchester, UK
Information: Conference Coordinates, Confer House, 69 Kingston Road, New Malden, Surrey KT3 3PB

24–25 October 1987
Autumn '87 Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, c/o Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

1–6 November 1987
Progress in Cancer Management: Radiotherapy and Chemotherapy
London, UK
Information: Courses Department, The British Council, 65 Davies Street, London, W1Y 2AA, UK

5–6 November 1987
Annual Joint Scientific Meeting of the American Pancreatic Association and the Pancreas Cancer Section of the NCI Organ Systems Program
Chicago, Illinois, USA
Information: Midge Kellerhaus, American Pancreatic Association, Department of Surgery, M580, University of Missouri Medical Center, Columbia, MO 65212, USA

6 November 1987
Colonoscopy Teaching Day for Beginners
Southampton, UK
Information: Peter McDonald, Lecturer in Surgery, Department of Surgery, F Level Centre Block, Southampton General Hospital, Tremona Road, Southampton SO1 6HU, UK

6 November 1987
12th Annual Meeting of the Pancreatic Society of Great Britain and Ireland
London, UK
Information: Mr C. W. Imrie, Consultant Surgeon, Royal Infirmary, Glasgow G4 0SF, UK

11–13 November 1987
First International Congress in Oral Cancer
Singapore
Information: Dr N. Ravindranathan, The Secretariat Department of Oral Surgery, Faculty of Dentistry, National University of Singapore, Kent Ridge, Singapore

12–14 November 1987
Seventh Annual William Beaumont Army Medical Center Trauma Symposium: Controversies in Head and Neck Trauma
El Paso, Texas, USA
Information: LtC Troy M. Reyna, MD, Chief, Trauma Service, William Beaumont Army Medical Center, El Paso, Texas 79920-5001, USA

13–15 November 1987
14th Annual Symposium on Current Critical Problems and New Horizons in Vascular Surgery
New York, USA
Information: Continuing Medical Education, Albert Einstein College of Medicine, Montefiore Medical Center, 3301 Bainbridge Avenue, Bronx, New York 10467, USA

15–18 November 1987
All Americas Health '87
Tampa, Florida, USA
Information: Denis Beckett, Fairs and Exhibition Ltd, 51 Doughty Street, Gray's Inn, London WC1N 2LB, UK

16–20 November 1987
Fourth International Symposium on Cardiorespiratory Emergencies
Rotterdam, The Netherlands
Information: Dr Omar Prakash, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands

1–2 December 1987
First International Symposium on Aids and the Surgeon
London, UK
Information: Ms Pauline Sleight, BDI Conferences Ltd, Kensington Business Centre, 9–11 Kensington High Street, London, W8 5NP, UK

23–24 January 1988
Hong Kong Surgical Forum Winter 1988
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

8–12 February 1988
Third Biennial Conference of the Indian Society of Oncology and the Indo–USSR International Workshop on Oesophageal Cancer
Bangalore, India
Information: Conference Secretariat: Kidwai Memorial Institute of Oncology, Hosur Road, Bangalore-560 029-India

13–15 April 1988
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Harrogate, UK
Information: Mr B. T. Jackson,, The Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

1–6 May 1988
Bicentennial Scientific Meeting Royal Australasian College of Surgeons
Brisbane, Australia
Information: 1988 GSM, Royal Australasian College of Surgeons, Spring Street, Melbourne, Australia 3000.

5–7 May 1988
Biennial Congress of the European Council of Coloproctology 1988
Geneva, Switzerland
Information: General Secretary of the European Council of Coloproctology, Policlinique de Chirurgie, Hôpital Cantonal Universitaire de Genève, 1211 Geneva 4, Switzerland

12–14 May 1988
Second Vienna Shock Forum
Vienna, Austria
Information: AUSTROPA Kongbressbüro, Friedrichstrasse 7, A-1010 Vienna, Austria

29 May–3 June 1988
Second World Congress on Hepato-Pancreato-Biliary Surgery
Amsterdam, The Netherlands
Information: Q. A. Laman Trip, Organizer, Alton House, Keizersgracht 792, 1017 EC Amsterdam, The Netherlands

12–17 June 1988
Cardiovascular and Interventional Radiological Society of Europe
Berlin, FRG
Information: Dr Reingard Sörensen, Klinikum Steglitz, Röntgendiagnostik, Hindenburgdamm 30, 1000 Berin 45, FRG

3–9 July 1988
16th World Congress of the International College of Surgeons
Milan, Italy
Information: Secretariat, Clinica Chirurgica III—Università degli Studi, Via F Sforza 35, 20122 Milan, Italy

11–19 September 1988
XIIth International Congress of the Transplantation Society of Australia and New Zealand
Sydney, Australia
Information: Dr B. Hall, Honorary Secretary, Transplantation Society of Australia and New Zealand, 145 Macquaire St, Sydney 2000 Australia

Notices

Volunteers needed for 3–6 weeks surgical appointments in overseas Mission Hospitals. Please contact: Mr M. W. Flowers, Accident and Emergency, General Infirmary, Great George Street, Leeds LS1 3EX.